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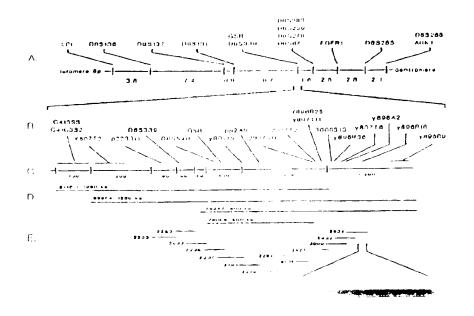
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(54) Title: GENES AND GENE PRODUCTS RELATED TO WERNER'S SYNDROME



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The present invention discloses nucleic acid molecules encoding WRN gene products, expression vectors and host cells suitable for 1 expressing such products.

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DESCRIPTION

GENES AND GENE PRODUCTS RELATED TO WERNER'S SYNDROME

5 TECHNICAL FIELD

The present invention relates generally to Werner's Syndrome and more specifically to methods and compositions suitable for use in diagnosis and treatment of Werner's Syndrome.

10 BACKGROUND OF THE INVENTION

Werner Syndrome (WS) is an autosomal recessive disorder with a complex phenotype. The disorder manifests itself in premature occurrence of agerelated diseases and premature appearance of some of the physical features of normal aging. The onset of symptoms usually occurs after adolescence. The disorder progresses throughout life and typically patients have a shortened life expectancy with a modal age of death at 47. The prevalence of Werner Syndrome is estimated for heterozygotes to be 1-5 per 1,000 individuals, and for homozygotes to be 1-22 per 1,000,000 individuals.

Clinical symptoms of Werner Syndrome include both a prevalence of age-related diseases and physical features of aging. Such diseases include arteriosclerosis and heart disease, both benign and malignant neoplasms (usually sarcomas), diabetes mellitus, osteoporosis, and ocular cataracts. The physical appearance of WS patients is often manifest as a short stature, premature graying or loss of hair, hypogonadism, altered skin pigmentation, hyperkeratosis, tight skin, bird-like facies, cutaneous atrophy, cutaneous leg ulcers, and telangiectasia. Most of these diseases and features are present in from 40-90% of WS patients. Diagnosis of WS relies mainly upon the appearance of a certain number of these diseases and features

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In addition to the noted signs and symptoms of aging. Werner Syndrome mimics normal aging as evidenced by the replicative potential of fibroblasts isolated from WS subjects. Replication potential of fibroblasts is reduced in these patients compared to fibroblasts isolated from age-matched controls, and is comparable to the replicative potential of fibroblasts taken from elderly subjects. Moreover, an increased mutation rate has been described in WS patients. Such abnormality is manifest as chromosomal instability, such as inversions, reciprocal translocations, deletions, and pseudodiploidy, and as increased mutation rate at the hypoxanthine phosphoribosyl transferase (HPRT) gene.

Werner Syndrome has been recognized as an autosomal recessive disorder. Goto et al., (Goto et al., Nature 355:735-738, 1992) mapped the WS gene onto the short arm of chromosome 8, using 21 affected Japanese families. The gene is located between marker D8S87 and ankyrin (ANK1). More recently, more refined mapping has pinpointed the WS gene to a region between marker D8S131 and D8S87, an 8.3 cM interval. Identification of the gene and gene product should add considerably to understanding the basis of Werner Syndrome and enable biochemical and genetic approaches to diagnosis and treatment.

The present invention provides a novel, previously unidentified gene for Werner Syndrome and compositions for diagnosis and treatment of WS, and further provides other related advantages.

SUMMARY OF THE INVENTION

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Briefly stated, the present invention provides isolated nucleic acid molecules encoding the WRN gene, as well as portions thereof, representative of which are provided in the Figures. The protein which is encoded by the WRN gene is referred to hereinafter as the "WRN protein". Within other embodiments, nucleic acid molecules are provided which encode a mutant WRN gene product that increases the

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Within other aspects of the present invention, isolated nucleic acid molecules are provided, selected from the group consisting of (a) an isolated nucleic acid molecule as set forth in the Figures, or complementary sequence thereof, (b) an isolated nucleic acid molecule that specifically hybridizes to the nucleic acid molecule of (a) under conditions of high stringency, and (c) an isolated nucleic acid that encodes a WRN gene product (WRN protein). As utilized herein, it should be understood that a nucleic acid molecule hybridizes "specifically" to an WRN gene (or related sequence) if it hybridizes detectably to such a sequence, but does not significantly or detectably hybridize to the Bloom's Syndrome gene (Ellis et al., Cell 83:655-666, 1995).

Within other aspects, expression vectors are provided comprising a promoter operably linked to one of the nucleic acid molecule described above. Representative examples of suitable promoters include tissue-specific promoters, as well as promoters such as the CMV I-E promoter, SV40 early promoter and MuLV LTR. Within related aspects, viral vectors are provided that are capable of directing the expression of a nucleic acid molecule as described above. Representative examples of such viral vectors include herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. Also provided are host cells (e.g., human, dog, monkey, rat or mouse cells) which carry the above-described vectors.

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Within other aspects of the present invention, isolated proteins or polypeptides are provided comprising a WRN gene product, as well as peptides of greater than 12, 13 or 20 amino acids. Within another embodiment, the protein is a mutant WRN gene product that increases the probability of Werner's Syndrome.

Within yet another aspect of the present invention, methods of treating or preventing Werner's Syndrome are provided (as well as for related diseases which are discussed in more detail below), comprising the step of administering to a patient a vector containing or expressing a nucleic acid molecule as described above, thereby reducing the likelihood or delaying the onset of Werner's Syndrome (or the related transport of the step of t

administering to a patient a protein as described above, thereby reducing the likelihood

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or delaying the onset of Werner's Syndrome (or a related disease) in the patient. Within certain embodiments, the above methods may be accomplished by *in vivo* administration.

Also provided by the present invention are pharmaceutical compositions comprising a nucleic acid molecule, vector, host cell, protein, or antibody as described above, along with a pharmaceutically acceptable carrier or diluent.

Within other aspects of the present invention, antibodies are provided which specifically bind to an WRN protein or to unique peptides derived therefrom. As utilized herein, it should be understood that an antibody is specific for an WRN protein (or peptide) if it binds detectably, and with a K_d of 10⁻⁷M or less (e.g., 10⁻⁸M, 10⁻⁹M, etc.), but does not bind detectably (or with an affinity of greater than 10⁻⁷M, (e.g., 10⁻⁶M, 10⁻⁵M, etc.) to an unrelated helicase (e.g., the Bloom's Syndrome gene, *supra*). Also provided are hybridomas which are capable of producing such antibodies.

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Within other aspects of the present invention, nucleic acid probes are provided which are capable of specifically hybridizing (as defined below) to an WRN gene under conditions of high stringency. Within one related aspect, such probes comprise at least a portion of the nucleotide sequence shown in the Figures, or its complementary sequence, the probe being capable of specifically hybridizing to a mutant WRN gene under conditions of high stringency. Representative probes of the present invention are generally at least 12 nucleotide bases in length, although they may be 14, 16, 18 bases or longer. Also provided are primer pairs capable of specifically amplifying all or a portion of any of the nucleic acid molecules disclosed herein.

Within other aspects of the invention, methods are provided for diagnosing a patient having an increased likelihood of contracting Werner's Syndrome (or a related disease), comprising the steps of (a) obtaining from a patient a biological sample containing nucleic acid, (b) incubating the nucleic acid with a probe which is capable of specifically hybridizing to a mutant WRN gene under condition and for

of contracting Werner's Syndrome (or a related disease). Within another aspect,

methods are provided comprising the steps of (a) obtaining from a patient a biological sample containing nucleic acid, (b) amplifying a selected nucleic acid sequence associated with a mutant WRN gene, and (c) detecting the presence of an amplified nucleic acid sequence, and thereby determining that the patient has an increased likelihood of contracting Werner's Syndrome (or a related disease). Suitable biological samples include nucleated cells obtained from the peripheral blood, from buccal swabs, or brain tissue.

Within another aspect, peptide vaccines are provided which comprise a portion of a mutant WRN gene product containing a mutation, in combination with a pharmaceutically acceptable carrier or diluent.

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Within yet another aspect, transgenic animals are provided whose germ cells and somatic cells contain a WRN gene (or lack thereof, i.e., a "knockout") which is operably linked to a promoter effective for the expression of the gene, the gene being introduced into the animal, or an ancestor of the animal, at an embryonic stage. Within one embodiment, the animal is a mouse, rat or dog. Within other embodiments, the WRN gene is expressed from a vector as described above. Within yet another embodiment, the WRN gene encodes a mutant WRN gene product.

These and other aspects of the present invention will become evident upon reference to the following detailed description and attached drawings. In addition, various references are set forth herein which describe in more detail certain procedures or compositions ($e\,g$, plasmids, etc.), and are therefore incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE LISTING

Figure 1 is a genetic and physical map of the WRN region. The genetic map (A) of the region is sex-equal with distances given in cM. The polymorphic loci used (B) are di-nucleotide and tri-nucleotide repeat STRP loci. The physical map

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^{2253, 3833, 2236,} and 3101. Marker order was determined from the sequence-tagged

site (STS) content of YACs, P1 clones, and cosmid clones and from genomic DNA sequence from P1 clones. The YACs presented (D) represent the minimal tiling and are the YACs used for cDNA selection experiments. The P1 and cosmid clones needed for the minimum tiling path are shown (E). Clones shown are P1 clones except for 8C11, which is a cosmid clone. Clone order was established by STS content.

Figures 2A and 2B are the DNA (SEQ ID No. 70) and predicted amino acid (SEQ ID No. 71) sequences of the WRN gene transcript. The one-letter amino acid code is used in Fig. 2B.

Figures 3A-3C are the DNA and predicted amino acid sequence of an alternate WRN gene transcript (SEQ ID Nos. 72 and 73).

Figures 4A-4G are an alignment of the WRN gene product (SEQ ID No. 74) with known helicases from *S. pombe* (SEQ ID No. 76), *E. coli* (SEQ ID No. 75), human (SEQ ID No. 77) and the Bloom's Syndrome gene "BLM" (SEQ ID No. 78).

Figures 5A-5U are the genomic DNA sequence of the region containing a WRN gene (SEQ ID No. 79).

Figure 6 presents a cDNA sequence of the mouse WRN gene (SEQ ID Nos. 205 and 206).

Figure 7 is a genomic DNA sequence of the mouse WRN gene (SEQ ID Nos. 207-209).

Figure 8 is a diagram of the WRN gene product with location of mutations. A, WRN cDNA. Numbering across the top refers to the cDNA sequence as numbered in GenBank L76937. B, Predicted WRN gene product. The helicase domain is designated as "HD", motifs from I to VI are indicated. C, Location of mutations. Numbering across the bottom refer to the mutations. *: nonsense mutation. ^: frame shift mutation caused by a single base deletion. Gray lines: frame shift mutations causing deletion of exon(s). D, Predicted proteins. Lines represent the different predicted transacted proteins are found from mutation.

³⁰ the size of cells (panel C) expressing the WRN gene.

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Figure 10 shows the alignment of the mouse and human WRN gene products.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Prior to setting forth the invention in detail, it may be helpful to an understanding thereof to set forth definitions of certain terms and to list and to define the abbreviations that will be used hereinafter.

"Genetic marker" is any segment of a chromosome that is distinguishably unique in the genome, and polymorphic in the population so as to provide information about the inheritance of linked DNA sequences, genes and/or other markers.

"Vector" refers to an assembly which is capable of directing the expression of a WRN gene, as well as any additional sequence(s) or gene(s) of interest. The vector must include transcriptional promoter elements which are operably linked to the genes of interest. The vector may be composed of either deoxyribonucleic acids ("DNA"), ribonucleic acids ("RNA"), or a combination of the two (e.g., a DNA-RNA chimeric). Optionally, the vector may include a polyadenylation sequence, one or more restriction sites, as well as one or more selectable markers such as neomycin phosphotransferase or hygromycin phosphotransferase. Additionally, depending on the host cell chosen and the vector employed, other genetic elements such as an origin of replication, additional nucleic acid restriction sites, enhancers, sequences conferring inducibility of transcription, and selectable markers, may also be incorporated into the vectors described herein.

Abbreviations: YAC, yeast artificial chromosome: EST, expressed sequence tag; PCR, polymerase chain reaction; RT-PCR, PCR process in which RNA is first transcribed into DNA at the first step using reverse transcriptase (RT); cDNA, any

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compositions for the detection and treatment of Werner's Syndrome, as well as related

diseases. These methods and compositions include a family of Werner's Syndrome-related genes, and the proteins encoded thereby, that have been implicated in the onset of Werner's Syndrome. These genes and proteins, including genetic markers, nucleic acid sequences and clones, are also useful in the creation of *in vitro* and animal models and screening tests useful for the study of Werner's Syndrome, including the possible identification of other genes implicated in Werner's Syndrome. The present invention also provides vector constructs, genetic markers, nucleic acid sequences, clones, diagnostic tests and compositions and methods for the identification of individuals likely to suffer from Werner's Syndrome.

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Genes and Gene Products Related To Werner's Syndrome

The present invention provides isolated nucleic acid molecules comprising a portion of the gene which is implicated in the onset of WS. Briefly, as can be seen from Figure 4, this gene encodes a protein that is similar in amino acid sequence to several known ATP-dependent DNA helicases (enzymes that unwind the DNA duplex). It is less similar to known RNA-DNA helicases. Helicases are involved in the replication of DNA, often binding the replication origin, and/or the replication complex. In addition, the single stranded DNA that is involved in recombination can be generated by DNA helicases.

Although various aspects of the WRN gene (or portions thereof) are shown in the Figures, it should be understood that within the context of the present invention, reference to one or more of these genes includes derivatives of the genes that are substantially similar to the genes (and, where appropriate, the proteins (including peptides and polypeptides) that are encoded by the genes and their derivatives). As used herein, a nucleotide sequence is deemed to be "substantially similar" if: (a) the nucleotide sequence is derived from the coding region of the described genes and

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includes, for example, portions of the sequence or allelic variations of the sequences

hypridization to nucleotide sequences of the present invention under high or very high

stringency (see Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, NY, 1989); or (c) the nucleic acid sequences are degenerate as a result of the genetic code to the nucleic acid sequences defined in (a) or (b). Further, the nucleic acid molecule disclosed herein includes both complementary and non-complementary sequences, provided the sequences otherwise meet the criteria set forth herein. Within the context of the present invention, high stringency means standard hybridization conditions (e.g., 5x SSPE, 0.5% SDS at 65°C, or the equivalent) while very high stringency means conditions of hybridization such that the nucleotide sequence is able to selectively hybridize to a single allele of the WS-related gene

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The WRN gene may be isolated from genomic DNA or cDNA. Genomic DNA libraries constructed in chromosomal vectors, such as YACs (yeast artificial chromosomes), bacteriophage vectors, such as λEMBL3, λgt10, cosmids, or plasmids are suitable for use. cDNA libraries constructed in bacteriophage vectors. plasmids, or others, are suitable for screening. Such libraries may be constructed using methods and techniques known in the art (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, 1989) or purchased from commercial sources (e.g., Clontech, Palo Alto, CA). Within one embodiment, the WRN gene is isolated by PCR performed on genomic DNA, cDNA or DNA from libraries, or is isolated by probe hybridization of genomic DNA or cDNA libraries. Primers for PCR and probes for hybridization screening may be designed based on the DNA sequence of WRN presented herein. The DNA sequence of a portion of the WRN gene and the entire coding sequence is presented in the Figures. Primers for PCR should be derived from sequences in the 5' and 3' untranslated region in order to isolate a full-length The primers should not have self-complementary sequences nor have complementary sequences at their 3' end (to prevent primer-dimer formation). Preferably, the primers have a GC content of about 50% and contain restriction sites. The primers are annealed to cDNA and sufficient cycles of PCR are performed to yield

gropagated. An organicieotide hybridization probe suitable for screening genomic or

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cDNA libraries may be designed based on the sequence provided herein. Preferably, the oligonucleotide is 20-30 bases long. Such an oligonucleotide may be synthesized by automated synthesis. The oligonucleotide may be conveniently labeled at the 5' end with a reporter molecule, such as a radionuclide, (e.g., 32P) or biotin. The library is plated as colonies or phage, depending upon the vector, and the recombinant DNA is transferred to nylon or nitrocellulose membranes. Following denaturation, neutralization, and fixation of the DNA to the membrane, the membranes are hybridized with the labeled probe. The membranes are washed and the reporter molecule detected. The hybridizing colonies or phage are isolated and propagated. Candidate clones or PCR amplified fragments may be verified as containing WRN DNA by any of various means. For example, the candidate clones may be hybridized with a second, nonoverlapping probe or subjected to DNA sequence analysis. In these ways, clones containing WRN gene, which are suitable for use in the present invention are isolated.

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The structure of the proteins encoded by the nucleic acid molecules described herein may be predicted from the primary translation products using the hydrophobicity plot function of, for example, P/C Gene, Lasergen System, DNA STAR. Madison, Wisconsin, or according to the methods described by Kyte and Doolittle (J. Mol. Biol. 157:105-132, 1982).

WRN proteins of the present invention may be prepared in the form of acidic or basic salts, or in neutral form. In addition, individual amino acid residues may be modified by oxidation or reduction. Furthermore, various substitutions, deletions, or additions may be made to the amino acid or nucleic acid sequences, the net effect of which is to retain or further enhance or decrease the biological activity of the mutant or wild-type protein. Moreover, due to degeneracy in the genetic code, for example, there may be considerable variation in nucleotide sequences encoding the same amino acid sequence.

Other derivatives of the WRN proteins disclosed herein include

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which may be added to facilitate purification or identification of WRN proteins (see

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U.S. Patent No. 4,851,341; see also. Hopp et al., Bio/Technology 6:1204, 1988.) Alternatively, fusion proteins such as WRN protein-β-galactosidase or WRN protein-luciferase may be constructed in order to assist in the identification, expression, and analysis of WRN proteins.

WRN proteins of the present invention may be constructed using a wide variety of techniques described herein. Further, mutations may be introduced at particular loci by synthesizing oligonucleotides containing a mutant sequence, flanked by restriction sites enabling ligation to fragments of the native sequence. Following ligation, the resulting reconstructed sequence encodes a derivative having the desired amino acid insertion, substitution, or deletion.

Alternatively, oligonucleotide-directed site-specific (or segment specific) mutagenesis procedures may be employed to provide an altered gene having particular codons altered according to the substitution, deletion, or insertion required. Exemplary methods of making the alterations set forth above are disclosed by Walder et al. (Gene 42:133, 1986); Bauer et al. (Gene 37:73, 1985); Craik (BioTechniques, January 1985, 12-19); Smith et al. (Genetic Engineering: Principles and Methods, Plenum Press, 1981); and Sambrook et al. (supra). Deletion or truncation derivatives of WRN proteins (e.g., a soluble extracellular portion) may also be constructed by utilizing convenient restriction endonuclease sites adjacent to the desired deletion. Subsequent to restriction, overhangs may be filled in, and the DNA religated. Exemplary methods of making the alterations set forth above are disclosed by Sambrook et al. (Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory Press, 1989).

Mutations of the present invention preferably preserve the reading frame of the coding sequences. Furthermore, the mutations will preferably not create complementary regions that could hybridize to produce secondary mRNA structures, such as loops or hairpins, that would adversely affect translation of the mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the

target codon and the expressed mutants screened for indicative biological activity

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Alternatively, mutations may be introduced at particular loci by synthesizing oligonucleotides containing a mutant sequence, flanked by restriction sites enabling ligation to fragments of the native sequence. Following ligation, the resulting reconstructed sequence encodes a derivative having the desired amino acid insertion, substitution, or deletion.

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WRN proteins may also be constructed utilizing techniques of PCR mutagenesis, chemical mutagenesis (Drinkwater and Klinedinst, *PNAS* 83:3402-3406, 1986), by forced nucleotide misincorporation (e.g., Liao and Wise *Gene* 88:107-111, 1990), or by use of randomly mutagenized oligonucleotides (Horwitz et al., *Genome* 3:112-117, 1989).

Proteins can be isolated by, among other methods, culturing suitable host and vector systems to produce the recombinant translation products of the present invention. Supernates from such cell lines, or protein inclusions or whole cells where the protein is not excreted into the supernate, can then be treated by a variety of purification procedures in order to isolate the desired proteins. For example, the supernate may be first concentrated using commercially available protein concentration filters, such as an Amicon or Millipore Pellicon ultrafiltration unit. Following concentration, the concentrate may be applied to a suitable purification matrix such as, for example, an anti-protein antibody bound to a suitable support. Alternatively, anion or cation exchange resins may be employed in order to purify the protein. As a further alternative, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps may be employed to further purify the protein. Other methods of isolating the proteins of the present invention are well known in the skill of the art.

A protein is deemed to be "isolated" within the context of the present invention if no other (undesired) protein is detected pursuant to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis followed by Coomassie blue staining. Within other embodiments, the desired protein can be isolated such that no

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Expression of a WRN gene

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The present invention also provides for the manipulation and expression of the above described genes by culturing host cells containing a vector capable of expressing the above-described genes. Such vectors or vector constructs include either synthetic or cDNA-derived nucleic acid molecules encoding WRN proteins, which are operably linked to suitable transcriptional or translational regulatory elements. Suitable regulatory elements may be derived from a variety of sources, including bacterial, fungal, viral, mammalian, insect, or plant genes. Selection of appropriate regulatory elements is dependent on the host cell chosen, and may be readily accomplished by one of ordinary skill in the art. Examples of regulatory elements include: a transcriptional promoter and enhancer or RNA polymerase binding sequence, a transcriptional terminator, and a ribosomal binding sequence, including a translation initiation signal.

Nucleic acid molecules that encode any of the WRN proteins described above may be readily expressed by a wide variety of prokaryotic and eukaryotic host cells, including bacterial, mammalian, yeast or other fungi, viral, insect. or plant cells. Methods for transforming or transfecting such cells to express foreign DNA are well known in the art (see, e.g., Itakura et al., U.S. Patent No. 4,704,362; Hinnen et al., *Proc. Natl. Acad. Sci. USA 75*:1929-1933, 1978; Murray et al., U.S. Patent No. 4,801,542; Upshall et al., U.S. Patent No. 4,935,349; Hagen et al., U.S. Patent No. 4,784,950; Axel et al., U.S. Patent No. 4,399,216; Goeddel et al., U.S. Patent No. 4,766,075; and Sambrook et al. *Molecular Cloning: A Laboratory Manual*, 2nd edition. Cold Spring Harbor Laboratory Press, 1989; for plant cells see Czako and Marton, *Plant Physiol 104*:1067-1071, 1994; and Paszkowski et al., *Biotech. 24*:387-392, 1992).

Bacterial host cells suitable for carrying out the present invention include E. coli, B. subtilis, Salmonella typhimurium, and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus, as well as many other bacterial species well known to one of ordinary skill in the art. Representative examples of

Canctions in the host cell, one or more selectable phenotypic markers, and a bacterial

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origin of replication. Representative promoters include the β-lactamase (penicillinase) and lactose promoter system (see Chang et al., Nature 275:615, 1978), the T7 RNA polymerase promoter (Studier et al., Meth. Enzymol. 185:60-89, 1990), the lambda promoter (Elvin et al., Gene 87:123-126, 1990), the trp promoter (Nichols and Yanofsky, Meth. in Enzymology 101:155, 1983) and the tac promoter (Russell et al., Gene 20: 231, 1982). Representative selectable markers include various antibiotic resistance markers such as the kanamycin or ampicillin resistance genes. Many plasmids suitable for transforming host cells are well known in the art, including among others. pBR322 (see Bolivar et al., Gene 2:95, 1977), the pUC plasmids pUC18, pUC19, pUC118, pUC119 (see Messing, Meth. in Enzymology 101:20-77, 1983 and Vieira and Messing, Gene 19:259-268, 1982), and pNH8A, pNH16a, pNH18a, and Bluescript M13 (Stratagene, La Jolla, Calif.).

Yeast and fungi host cells suitable for carrying out the present invention include, among others, Saccharomyces pombe, Saccharomyces cerevisiae, the genera Pichia or Kluyveromyces and various species of the genus Aspergillus (McKnight et al., U.S. Patent No. 4,935,349). Suitable expression vectors for yeast and fungi include, among others, YCp50 (ATCC No. 37419) for yeast, and the amdS cloning vector pV3 (Turnbull, Bio/Technology 7:169, 1989), YRp7 (Struhl et al., Proc. Natl. Acad. Sci. USA 76:1035-1039, 1978), YEp13 (Broach et al., Gene 8:121-133, 1979), pJDB249 and pJDB219 (Beggs, Nature 275:104-108, 1978) and derivatives thereof.

Preferred promoters for use in yeast include promoters from yeast glycolytic genes (Hitzeman et al., *J. Biol. Chem. 255*:12073-12080, 1980; Alber and Kawasaki, *J. Mol. Appl. Genet. 1*:419-434, 1982) or alcohol dehydrogenase genes (Young et al., in *Genetic Engineering of Microorganisms for Chemicals*, Hollaender et al. (eds.), p. 355, Plenum, New York, 1982; Ammerer, *Meth. Enzymol. 101*:192-201, 1983). Examples of useful promoters for fungi vectors include those derived from *Aspergillus nidulans* glycolytic genes, such as the *adh3* promoter (McKnight et al.

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As with bacterial vectors, the yeast vectors will generally include a selectable marker, which may be one of any number of genes that exhibit a dominant phenotype for which a phenotypic assay exists to enable transformants to be selected. Preferred selectable markers are those that complement host cell auxotrophy, provide antibiotic resistance or enable a cell to utilize specific carbon sources, and include *leu2* (Broach et al., *ibid.*), *ura3* (Botstein et al., *Gene 8:17*, 1979), or *his3* (Struhl et al., *ibid.*). Another suitable selectable marker is the *cat* gene, which confers chloramphenicol resistance on yeast cells.

Techniques for transforming fungi are well known in the literature, and have been described, for instance, by Beggs (*ibid.*), Hinnen et al. (*Proc. Natl. Acad. Sci. USA 75*:1929-1933, 1978), Yelton et al. (*Proc. Natl. Acad. Sci. USA 81*:1740-1747, 1984), and Russell (*Nature 301*:167-169, 1983). The genotype of the host cell may contain a genetic defect that is complemented by the selectable marker present on the expression vector. Choice of a particular host and selectable marker is well within the level of ordinary skill in the art.

Protocols for the transformation of yeast are also well known to those of ordinary skill in the art. For example, transformation may be readily accomplished either by preparation of spheroplasts of yeast with DNA (see Hinnen et al., PNAS USA 75:1929, 1978) or by treatment with alkaline salts such as LiCl (see Itoh et al., J Bacteriology 153:163, 1983). Transformation of fungi may also be carried out using polyethylene glycol as described by Cullen et al. (Bio/Technology 5:369, 1987).

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Viral vectors include those which comprise a promoter that directs the expression of an isolated nucleic acid molecule that encodes an WRN protein as described above. A wide variety of promoters may be utilized within the context of the present invention, including for example, promoters such as MoMLV LTR, RSV LTR. Friend MuLV LTR, adenoviral promoter (Ohno et al., *Science* 265: 781-784, 1994), neomycin phosphotransferase promoter/enhancer, late parvovirus promoter (Koering

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promoter, and the cytomegalovirus immediate late promoter. Within particularly

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preferred embodiments of the invention, the promoter is a tissue-specific promoter (see e.g., WO 91/02805; EP 0,415,731; and WO 90/07936). Representative examples of suitable tissue specific promoters include neural specific enolase promoter, platelet derived growth factor beta promoter, bone morpho-genetic protein promoter, human alphal-chimaerin promoter, synapsin I promoter and synapsin II promoter. In addition to the above-noted promoters, other viral-specific promoters (e.g., retroviral promoters (including those noted above, as well as others such as HIV promoters), hepatitis, herpes (e.g., EBV), and bacterial, fungal or parasitic (e.g., malarial) -specific promoters may be utilized in order to target a specific cell or tissue which is infected with a virus, bacteria, fungus or parasite.

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Thus, WRN proteins of the present invention may be expressed from a variety of viral vectors, including for example, herpes viral vectors (e.g., U.S. Patent No. 5,288,641), adenoviral vectors (e.g., WO 94/26914, WO 93/9191; Kolls et al., PNAS 91(1):215-219, 1994; Kass-Eisler et al., PNAS 90(24):11498-502, 1993; Guzman et al., Circulation 88(6):2838-48, 1993; Guzman et al., Cir. Res 73(6):1202-1207, 1993; Zabner et al., Cell 75(2):207-216, 1993; Li et al., Hum Gene Ther. 4(4):403-409. 1993; Caillaud et al., Eur. J. Neurosci. 5(10:1287-1291, 1993; Vincent et al., Nat. Genet. 5(2):130-134, 1993; Jaffe et al., Nat. Genet. 1(5):372-378, 1992; and Levrero et al, Gene 101(2):195-202, 1991), adeno-associated viral vectors (WO 95/13365; Flotte et al., PNAS 90(22):10613-10617, 1993), baculovirus vectors, parvovirus vectors (Koering et al., Hum. Gene Therap. 5:457-463, 1994), pox virus vectors (Panicali and Paoletti, PNAS 79:4927-4931, 1982; and Ozaki et al., Biochem. Biophys Res Comm. 193(2):653-660, 1993), and retroviruses (e.g., EP 0,415,731; WO 90/07936; WO 91/0285, WO 94/03622; WO 93/25698; WO 93/25234; U.S. Patent No. 5,219,740; WO 93/11230; WO 93/10218. Viral vectors may likewise be constructed which contain a mixture of different elements (e.g., promoters, envelope sequences and the like) from different viruses, or non-viral sources. Within various embodiments, either the viral

Mammalian cells suitable for carrying out the present invention include, among others: PC12 (ATCC No. CRL1721), N1E-115 neuroblastoma, SK-N-BE(2)C neuroblastoma, SHSY5 adrenergic neuroblastoma, NS20Y and NG108-15 murine cholinergic cell lines, or rat F2 dorsal root ganglion line, COS (e.g., ATCC No. CRL 1650 or 1651), BHK (e.g., ATCC No. CRL 6281; BHK 570 cell line (deposited with the American Type Culture Collection under accession number CRL 10314). CHO (ATCC No. CCL 61), HeLa (e.g., ATCC No. CCL 2), 293 (ATCC No. 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and NS-1 cells. Other mammalian cell lines may be used within the present invention. including Rat Hep I (ATCC No. CRL 1600), Rat Hep II (ATCC No. CRL 1548), TCMK (ATCC No. CCL 139), Human lung (ATCC No. CCL 75.1), Human hepatoma (ATCC No. HTB-52), Hep G2 (ATCC No. HB 8065), Mouse liver (ATCC No. CCL 29.1), NCTC 1469 (ATCC No. CCL 9.1). SP2/0-Ag14 (ATCC No. 1581), HIT-T15 (ATCC No. CRL 1777), and RINm 5AHT₂B (Orskov and Nielson, FEBS 229(1):175-178, 1988).

Mammalian expression vectors for use in carrying out the present invention will include a promoter capable of directing the transcription of a cloned gene or cDNA. Preferred promoters include viral promoters and cellular promoters. Viral promoters include the cytomegalovirus immediate early promoter (Boshart et al., Cell 41:521-530, 1985), cytomegalovirus immediate late promoter. SV40 promoter (Subramani et al., Mol. Cell. Biol. 1:854-864, 1981), MMTV LTR, RSV LTR, metallothionein-1, adenovirus E1a. Cellular promoters include the mouse metallothionein-1 promoter (Palmiter et al., U.S. Patent No. 4.579.821), a mouse V_K promoter (Bergman et al., Proc. Natl. Acad. Sci. USA 81:7041-7045, 1983; Grant et al., Nucl. Acids Res. 15:5496, 1987) and a mouse V_H promoter (Loh et al., Cell 33:85-93, 1983). The choice of promoter will depend, at least in part, upon the level of expression desired or the recipient cell line to be transfected.

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Such expression vectors may also contain a set of RNA splice sites

adenovirus and or immunoglobulin genes. Also contained in the expression vectors is a

polyadenylation signal located downstream of the coding sequence of interest. Suitable polyadenylation signals include the early or late polyadenylation signals from SV40 (Kaufman and Sharp, *ibid.*), the polyadenylation signal from the Adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto et al., *Nuc. Acids Res.* 9:3719-3730, 1981). The expression vectors may include a noncoding viral leader sequence, such as the Adenovirus 2 tripartite leader, located between the promoter and the RNA splice sites. Preferred vectors may also include enhancer sequences, such as the SV40 enhancer. Expression vectors may also include sequences encoding the adenovirus VA RNAs. Suitable expression vectors can be obtained from commercial sources (e.g., Stratagene, La Jolla, Calif.).

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Vector constructs comprising cloned DNA sequences can be introduced into cultured mammalian cells by, for example, calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981; Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), or DEAE-dextran mediated transfection (Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley and Sons, Inc., NY, 1987). To identify cells that have stably integrated the cloned DNA, a selectable marker is generally introduced into the cells along with the gene or cDNA of interest. Preferred selectable markers for use in cultured mammalian cells include genes that confer resistance to drugs, such as neomycin, hygromycin, and methotrexate. The selectable marker may be an amplifiable selectable marker. Preferred amplifiable selectable markers are the DHFR gene and the neomycin resistance gene. Selectable markers are reviewed by Thilly (Mammalian Cell Technology, Butterworth Publishers, Stoneham, MA, which is incorporated herein by reference).

Mammalian cells containing a suitable vector are allowed to grow for a period of time, typically 1-2 days, to begin expressing the DNA sequence(s) of interest. Drug selection is then applied to select for growth of cells that are expressing the

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manner to select for increased copy number of the cloned sequences, thereby increasing

expression levels. Cells expressing the introduced sequences are selected and screened for production of the protein of interest in the desired form or at the desired level. Cells that satisfy these criteria can then be cloned and scaled up for production.

Protocols for the transfection of mammalian cells are well known to those of ordinary skill in the art. Representative methods include calcium phosphate mediated transfection, electroporation, lipofection, retroviral, adenoviral and protoplast fusion-mediated transfection (see Sambrook et al., supra). Naked vector constructs can also be taken up by muscular cells or other suitable cells subsequent to injection into the muscle of a mammal (or other animals).

Numerous insect host cells known in the art can also be useful within the present invention, in light of the subject specification. For example, the use of baculoviruses as vectors for expressing heterologous DNA sequences in insect cells has been reviewed by Atkinson et al. (*Pestic. Sci. 28*:215-224,1990).

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Numerous plant host cells known in the art can also be useful within the present invention, in light of the subject specification. For example, the use of *Agrobacterium rhizogenes* as vectors for expressing genes in plant cells has been reviewed by Sinkar et al., (*J. Biosci. (Bangalore) 11*:47-58, 1987).

WRN proteins may be prepared by growing (typically by culturing) the host/vector systems described above, in order to express the recombinant WRN proteins. Recombinantly produced WRN proteins may be further purified as described in more detail below.

Within related aspects of the present invention. WRN proteins may be expressed in a transgenic animal whose germ cells and somatic cells contain a WRN gene which is operably linked to a promoter effective for the expression of the gene. Alternatively, in a similar manner transgenic animals may be prepared that lack the WRN gene (e.g., "knockout" mice). Such transgenics may be prepared in a variety non-human animals, including mice, rats, rabbits, sheep, dogs, goats and pigs (see Hammer

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41:343-345, 1985 and U.S. Patent Nos. 5,175,383, 5,087,571, 4,736,866, 5,387,742, 5,347,075, 5,221,778, and 5,175,384).

Briefly, an expression vector, including a nucleic acid molecule to be expressed together with appropriately positioned expression control sequences, is introduced into pronuclei of fertilized eggs, for example, by microinjection. Integration of the injected DNA is detected by blot analysis of DNA from tissue samples. It is preferred that the introduced DNA be incorporated into the germ line of the animal so that it is passed on to the animal's progeny. Tissue-specific expression may be achieved through the use of a tissue-specific promoter, or through the use of an inducible promoter, such as the metallothionein gene promoter (Palmiter et al., 1983, *ibid*), which allows regulated expression of the transgene.

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Vectors of the present invention may contain or express a wide variety of additional nucleic acid molecules in place of or in addition to an WRN protein as described above, either from one or several separate promoters. For example, the viral vector may express a lymphokine or lymphokine receptor, antisense or ribozyme sequence or toxins. Representative examples of lymphokines include IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, GM-CSF, G-CSF, M-CSF, alpha-interferon, beta-interferon, gamma-interferon, and tumor necrosis factors, as well as their respective receptors. Representative examples of antisense sequences include antisense sequences which block the expression of WRN protein mutants. Representative examples of toxins include: ricin, abrin, diphtheria toxin, cholera toxin, saporin, gelonin, pokeweed antiviral protein, tritin. *Shigeila* toxin, and *Pseudomonas* exotoxin A.

Within other aspects of the invention, antisense oligonucleotide molecules are provided which specifically inhibit expression of mutant WRN nucleic acid sequences (see generally, Hirashima et al. in *Molecular Biology of RNA*. New Perspectives (M. Inouye and B. S. Dudock, eds., 1987 Academic Press. San Diego, p.

^{95 (969).} U.S. 5.359,951; WO 92 06693; and FP-A2-612844). Briefly, such

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molecules are constructed such that they are complementary to, and able to form Watson-Crick base pairs with, a region of transcribed WRN mutant mRNA sequence containing an WRN mutation. The resultant double-stranded nucleic acid interferes with subsequent processing of the mRNA, thereby preventing protein synthesis.

Within other related aspects of the invention, ribozyme molecules are provided wherein an antisense oligonucleotide sequence is incorporated into a ribozyme which can specifically cleave mRNA molecules transcribed from a mutant WRN gene (see generally, Kim et al. Proc. Nat. Acad. Sci. USA 84:8788 (1987); Haseloff, et al. Nature 234:585 (1988), Cech, JAMA 260:3030 (1988); Jeffries, et al. Nucleic Acids Res. 17:1371 (1989); U.S. 5,093,246; U.S. 5,354,855, U.S. 5,144,019; U.S. 5,272,262; U.S. 5,254.678; and U.S. 4,987,071). According to this aspect of the invention, the antisense sequence which is incorporated into a ribozyme includes a sequence complementary to, and able to form Watson-Crick base pairs with, a region of the transcribed mutant WRN mRNA containing an WRN mutation. The antisense sequence thus becomes a targeting agent for delivery of catalytic ribozyme activity specifically to mutant WRN mRNA, where such catalytic activity cleaves the mRNA to render it incapable of being subsequently processed for WRN protein translation.

Host Cells

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As discussed above, nucleic acid molecules which encode the WRN proteins of the present invention (or the vectors which contain and/or express related mutants) may readily be introduced into a wide variety of host cells. Representative examples of such host cells include plant cells, eukaryotic cells, and prokaryotic cells. Within preferred embodiments, the nucleic acid molecules are introduced into cells from a vertebrate or warm-blooded animal, such as a human, macaque, dog, cow, horse, pig, sheep, rat, hamster, mouse or fish cell, or any hybrid thereof.

Preferred prokaryotic host cells for use within the present invention

¹⁴⁴ cace coined therein are well known in the artisee, e.g., Maniatis et al., Molecular

Cloning A Laboratory Manual, Cold Spring Harbor Laboratory, 1982, which is incorporated herein by reference: or Sambrook et al., supra). Vectors used for expressing cloned DNA sequences in bacterial hosts will generally contain a selectable marker, such as a gene for antibiotic resistance, and a promoter that functions in the host ceil. Appropriate promoters include the trp (Nichols and Yanofsky, Meth. Enzymol. 101:155-164, 1983), lac (Casadaban et al., J. Bacteriol. 143:971-980, 1980), and phage λ (Queen, J. Mol. Appl. Genet. 2:1-10, 1983) promoter systems. Plasmids useful for transforming bacteria include the pUC plasmids (Messing, Meth. Enzymol. 101:20-78, 1983; Vieira and Messing, Gene 19:259 268, 1982), pBR322 (Bolivar et al., Gene 2:95-113, 1977), pCQV2 (Queen, ibid.), and derivatives thereof. Plasmids may contain both viral and bacterial elements.

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Preferred eukaryotic cells include cultured mammalian cell lines (e.g., rodent or human cell lines) and fungal cells, including species of yeast (e.g., Saccharomyces spp., particularly S. cerevisiae, Schizosaccharomyces spp., or Kluyveromyces spp.) or filamentous fungi (e.g., Aspergillus spp., Neurospora spp.). Strains of the yeast Saccharomyces cerevisiae are particularly preferred. Methods for producing recombinant proteins in a variety of prokaryotic and eukaryotic host cells are generally known in the art (see, "Gene Expression Technology," Methods in Enzymology, Vol. 185, Goeddel (ed.), Academic Press, San Diego, Calif., 1990; see also, "Guide to Yeast Genetics and Molecular Biology," Methods in Enzymology, Guthrie and Fink (eds.), Academic Press, San Diego, Calif., 1991). In general, a host cell will be selected on the basis of its ability to produce the protein of interest at a high level or its ability to carry out at least some of the processing steps necessary for the biological activity of the protein. In this way, the number of cloned DNA sequences that must be introduced into the host cell can be minimized and overall yield of biologically active protein can be maximized.

The nucleic acid molecules (or vectors) may be introduced into host cells

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Pearson, Somano Cell Gen. 7 603, 1981, Graham and Van der Eb. Virologi, 52:456,

1973), electroporation (Neumann et al., *EMBO J. 1*:841-845, 1982), retroviral, adenoviral, protoplast fusion-mediated transfection or DEAE-dextran mediated transfection (Ausubel et al., (eds.), *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc., NY, NY, 1987).

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Host cells containing vector constructs of the present invention are then cultured to express a DNA molecule as described above. The cells are cultured according to standard methods in a culture medium containing nutrients required for growth of the chosen host cells. A variety of suitable media are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals, as well as other components, e.g., growth factors or serum, that may be required by the particular host cells. The growth medium will generally select for cells containing the DNA construct(s) by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker on the DNA construct or co-transfected with the DNA construct.

Suitable growth conditions for yeast cells, for example, include culturing in a chemically defined medium, comprising a nitrogen source, which may be a non-amino acid nitrogen source or a yeast extract, inorganic salts, vitamins and essential amino acid supplements at a temperature between 4°C and 37°C, with 30°C being particularly preferred. The pH of the medium is preferably maintained at a pH greater than 2 and less than 8, more preferably pH 5-6. Methods for maintaining a stable pH include buffering and constant pH control. Preferred agents for pH control include sodium hydroxide. Preferred buffering agents include succinic acid and Bis-Tris (Sigma Chemical Co., St. Louis, Mo.). Due to the tendency of yeast host cells to hyperglycosylate heterologous proteins, it may be preferable to express the nucleic acid molecules of the present invention in yeast cells having a defect in a gene required for asparagine-linked glycosylation. Such cells are preferably grown in a medium containing an osmotic stabilizer. A preferred osmotic stabilizer is sorbitol

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Cultured mammalian cells are generally cultured in commercially available serum-containing or serum-free media. Selection of a medium and growth conditions appropriate for the particular cell line used is well within the level of ordinary skill in the art.

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<u>Antibodies</u>

Antibodies to the WRN proteins discussed above may readily be prepared given the disclosure provided herein. Such antibodies may, within certain embodiments, specifically recognize wild type WRN protein rather than a mutant WRN protein, mutant WRN protein rather than wild type WRN protein, or equally recognize both the mutant and wild-type forms of WRN protein. Antibodies may be used for isolation of the protein, establishing intracellular localization of the WRN protein, inhibiting activity of the protein (antagonist), or enhancing activity of the protein (agonist). Knowledge of the intracellular location of the WRN gene product may be abnormal in patients with WRN mutations, thus allowing the development of a rapid screening assay. As well, assays for small molecules that interact with the WRN gene product will be facilitated by the development of antibodies and localization studies.

Within the context of the present invention, antibodies are understood to include monoclonal antibodies, polyclonal antibodies, anti-idiotypic antibodies, antibody fragments (e.g., Fab. and F(ab')₂, F_V variable regions, or complementarity determining regions). As discussed above, antibodies are understood to be specific against an WRN protein if it binds with a K_d of greater than or equal to $10^{-7}M$, preferably greater than of equal to $10^{-8}M$. The affinity of a monoclonal antibody or binding partner can be readily determined by one of ordinary skill in the art (see Seatchard, Ann. N.Y. Acad. Sci. 51:660-672, 1949).

Briefly, polyclonal antibodies may be readily generated by one of ordinary skill in the art from a variety of warm-blooded animals such as horses down

cross-linking with glutaraldehyde) is utilized to immunize the animal through

intraperitoneal, intramuscular, intraocular, or subcutaneous injections, an adjuvant such as Freund's complete or incomplete adjuvant. Merely as an example, a peptide corresponding to residues 1375 through 1387 of the WRN polypeptide sequence is used to raise a rabbit polyclonal antiserum. Following several booster immunizations, samples of serum are collected and tested for reactivity to the WRN protein or peptide. Particularly preferred polyclonal antisera will give a signal on one of these assays that is at least three times greater than background. Once the titer of the animal has reached a plateau in terms of its reactivity to the protein, larger quantities of antisera may be readily obtained either by weekly bleedings, or by exsanguingting the animal.

Monoclonal antibodies may also be readily generated using conventional techniques (see U.S. Patent Nos. RE 32,011, 4,902,614, 4,543,439, and 4.411,993 which are incorporated herein by reference; see also Monoclonal Antibodies. Hybridomas: A New Dimension in Biological Analyses, Plenum Press, Kennett, McKearn, and Bechtol (eds.), 1980, and Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988, which are also incorporated herein by reference).

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Briefly, within one embodiment a subject animal such as a rat or mouse is injected with an WRN protein or portion thereof as described above. The protein may be admixed with an adjuvant such as Freund's complete or incomplete adjuvant in order to increase the resultant immune response. Between one and three weeks after the initial immunization the animal may be reimmunized with another booster immunization, and tested for reactivity to the protein utilizing assays described above. Once the animal has reached a plateau in its reactivity to the injected protein, it is sacrificed, and organs which contain large numbers of B cells such as the spleen and lymph nodes are harvested.

Cells which are obtained from the immunized animal may be immortalized by transfection with a virus such as the Epstein-Barr virus (EBV) (see

suitanje invetoma cell in order to create a "hybridoma" which secretes monoclonal

antibody. Suitable myeloma lines include, for example, NS-1 (ATCC No. TIB 18), and P3X63 - Ag 8.653 (ATCC No. CRL 1580).

Following the fusion, the cells may be placed into culture plates containing a suitable medium, such as RPMI 1640, or DMEM (Dulbecco's Modified Eagles Medium) (JRH Biosciences, Lenexa, Kansas), as well as additional ingredients, such as fetal bovine serum (FBS, i.e., from Hyclone, Logan, Utah, or JRH Biosciences). Additionally, the medium should contain a reagent which selectively allows for the growth of fused spleen and myeloma cells such as HAT (hypoxanthine, aminopterin, and thymidine) (Sigma Chemical Co., St. Louis, Missouri). After about seven days, the resulting fused cells or hybridomas may be screened in order to determine the presence of antibodies which are reactive against an WRN protein. A wide variety of assays may be utilized to determine the presence of antibodies which are reactive against the proteins of the present invention, including for example countercurrent immunoelectrophoresis, radioimmunoassays, radioimmunoprecipitations, enzyme-linked immuno-sorbent assays (ELISA), dot blot assays, western blots, immunoprecipitation. Inhibition or Competition Assays, and sandwich assays (see U.S. Patent Nos. 4,376.110 and 4.486,530; see also Antibodies: A Laboratory Manual, Harlow and Lane (eds.). Cold Spring Harbor Laboratory Press, 1988). Following several clonal dilutions and reassays, a hybridoma producing antibodies reactive against the WRN protein may be isolated.

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Other techniques may also be utilized to construct monoclonal antibodies (see William D. Huse et al., "Generation of a Large Combinational Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281, December 1989; see also L. Sastry et al., "Cloning of the Immunological Repertoire in Escherichia coli for Generation of Monoclonal Catalytic Antibodies: Construction of a Heavy Chain Variable Region-Specific cDNA Library," Proc. Natl. Acad. Sci. USA 86.5728-5732, August 1989; see also Michelle Alting-Mees et al., "Monoclonal Antibody Expression

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La Jolia, California, which enables the production of antibodies through recombinant

techniques). Briefly, mRNA is isolated from a B cell population, and utilized to create heavy and light chain immunoglobulin cDNA expression libraries in the λ -ImmunoZap(H) and λ ImmunoZap(L) vectors. These vectors may be screened individually or co-expressed to form Fab fragments or antibodies (see Huse et al., supra: see also Sastry et al., supra). Positive plaques may subsequently be converted to a non-lytic plasmid which allows high level expression of monoclonal antibody fragments from E, coli.

Similarly, portions or fragments, such as Fab and Fv fragments, of antibodies may also be constructed utilizing conventional enzymatic digestion or recombinant DNA techniques to incorporate the variable regions of a gene which encodes a specifically binding antibody. Within one embodiment, the genes which encode the variable region from a hybridoma producing a monoclonal antibody of interest are amplified using nucleotide primers for the variable region. These primers may be synthesized by one of ordinary skill in the art, or may be purchased from commercially available sources. Stratacyte (La Jolla, Calif.) sells primers for mouse and human variable regions including, among others, primers for V_{Ha}, V_{Hb}, V_{Hc}, V_{Hd}, C_{H1}, V₁ and C₁ regions. These primers may be utilized to amplify heavy or light chain variable regions, which may then be inserted into vectors such as ImmunoZAPTM H or ImmunoZAPTM L (Stratacyte), respectively. These vectors may then be introduced into E. coli, yeast, or mammalian-based systems for expression. Utilizing these techniques, large amounts of a single-chain protein containing a fusion of the $V_{\rm H}$ and $V_{\rm L}$ domains may be produced (see Bird et al., Science 242:423-426, 1988). In addition, such techniques may be utilized to change a "murine" antibody to a "human" antibody. without altering the binding specificity of the antibody.

Once suitable antibodies have been obtained, they may be isolated or purified by many techniques well known to those of ordinary skill in the art (see Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor

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combination of these techniques.

Assavs

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Assays useful within the context of the present invention include those assays for detecting agonists or antagonists of WRN protein activity. Other assays are useful for the screening of peptide or organic molecule libraries. Still other assays are useful for the identification and/or isolation of nucleic acid molecules and/or peptides within the present invention, the identification of proteins that interact or bind the WRN protein, for diagnosis of a patient with an increased likelihood of contracting Werner's Syndrome, or for diagnosis of a patient with susceptibility to or manifestation of a WRN-related disease.

Nucleic Acid Based Diagnostic Tests

Briefly, another aspect of the present invention provides probes and primers for detecting the WRN genes and/or mutants thereof. In one embodiment of this aspect, probes are provided that are capable of specifically hybridizing to DNA or RNA of the WRN genes. For purposes of the present invention, probes are "capable of hybridizing" to DNA or RNA of the WRN gene if they hybridize to an WRN gene under conditions of either high or moderate stringency (see Sambrook et al., supra) but not significantly or detectably to the an unrelated helicase gene such as the Bloom's Syndrome gene (Ellis et al., Cell 83:655-666, 1995). Preferably, the probe hybridizes to suitable nucleotide sequences under high stringency conditions, such as hybridization in 5x SSPE. 1x Denhardt's solution, 0.1% SDS at 65°C, and at least one wash to remove unhybridized probe in the presence of 0.2x SSC, 1x Denhardt's solution, 0.1% SDS at 65°C. Except as otherwise provided herein, probe sequences are designed to allow hybridization to WRN genes, but not to DNA or RNA sequences from other genes. The probes are used, for example, to hybridize to nucleic acid that is present in a biological sample isolated from a patient. The hybridized probe is then detected thereby

hybridization. Alternatively, the WRN gene may be amplified and the amplified

product subjected to DNA sequencing. Mutants of WRN may be detected by DNA sequence analysis or hybridization with allele-specific oligonucleotide probes under conditions and for time sufficient to allow hybridization to the specific allele. Typically, the hybridization buffer and wash will contain tetramethyl ammonium chloride or the like (*see* Sambrook et al., *supra*).

Nucleic acid probes of the present invention may be composed of either deoxyribonucleic acids (DNA), ribonucleic acids (RNA), nucleic acid analogues (e.g., peptide nucleic acids), or any combination thereof, and may be as few as about 12 nucleotides in length, usually about 14 to 18 nucleotides in length, and possibly as large as the entire sequence of a WRN gene. Selection of probe size is somewhat dependent upon the use of the probe, and is within the skill of the art.

Suitable probes can be constructed and labeled using techniques that are well known in the art. Shorter probes of, for example, 12 bases can be generated synthetically and labeled with ^{32}P using T_4 polynucleotide kinase. Longer probes of about 75 bases to less than 1.5 kb are preferably generated by, for example, PCR amplification in the presence of labeled precursors such as $[\alpha^{-32}P]dCTP$, digoxigenindUTP, or biotin-dATP. Probes of more than 1.5 kb are generally most easily amplified by transfecting a cell with a plasmid containing the relevant probe, growing the transfected cell into large quantities, and purifying the relevant sequence from the transfected cells. (See Sambrook et al., supra.)

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Probes can be labeled by a variety of markers, including for example, radioactive markers, fluorescent markers, enzymatic markers, and chromogenic markers. The use of ³²P is particularly preferred for marking or labeling a particular probe.

It is a feature of this aspect of the invention that the probes can be utilized to detect the presence of WRN mRNA or DNA within a sample. However, if the relevant sample is present in only a limited number, then it may be beneficial to

equence menuding, for example, RNA amplification (see Lizardi et al.,

Bio/Technology 6:1197-1202, 1988; Kramer et al., Nature 339:401-402, 1989; Lomeli et al., Clinical Chem. 35(9):1826-1831, 1989; U.S. Patent No. 4,786,600), and DNA amplification utilizing LCR or polymerase chain reaction ("PCR") (see, U.S. Patent Nos. 4.683,195, 4,683,202, and 4,800,159) (see also U.S. Patent Nos. 4,876,187 and 5.011,769, which describe an alternative detection/amplification system comprising the use of scissile linkages), or other nucleic acid amplification procedures that are well within the level of ordinary skill in the art. With respect to PCR, for example, the method may be modified as known in the art. Transcriptional enhancement of PCR may be accomplished by incorporation of bacteriophage T7 RNA polymerase promoter sequences in one of the primary oligonucleotides, and immunoenzymatic detection of the products from the enhanced emitter may be effected using anti-RNA:DNA antibodies (Blais, Appl. Environ. Microbiol. 60:348-352, 1994). PCR may also be used in combination with reverse dot-blot hybridization (lida et al., FEMS Microbiol. Lett. 114:167-172, 1993). PCR products may be quantitatively analyzed by incorporation of dUTP (Duplaa et al., Anal. Biochem 212:229-236, 1993), and samples may be filter sampled for PCR-gene probe detection (Bej et al., Appl. Environ Microbiol. 57:3529-3534, 1991).

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Within a particularly preferred embodiment, PCR amplification is utilized to detect the WRN DNA. Briefly, as described in greater detail below, a DNA sample is denatured at 95°C in order to generate single-stranded DNA. The DNA sample may be a cDNA generated from RNA. Specific primers are then annealed to the single-stranded DNA at 37°C to 70°C, depending on the proportion of AT/GC in the primers. The primers are extended at 72°C with *Taq* DNA polymerase or other thermostable DNA polymerase in order to generate the opposite strand to the template. These steps constitute one cycle, which may be repeated in order to amplify the selected sequence. For greater specificity, nested PCR may be performed. In nested PCR, a second amplification is performed using a second set of primers derived from sequences.

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convenient size for determining their sequence. In a preferred embodiment, nested PCR is performed.

Within an alternative preferred embodiment. LCR amplification is utilized for amplification. LCR primers are synthesized such that the 5' base of the upstream primer is capable of hybridizing to a unique base pair in a desired gene to specifically detect an WRN gene.

Within another preferred embodiment, the probes are used in an automated, non-isotopic strategy wherein target nucleic acid sequences are amplified by PCR, and then desired products are determined by a colorimetric oligonucleotide ligation assay (OLA) (Nickerson et al., *Proc. Natl. Acad. Sci. USA 81*:8923-8927, 1990).

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Primers for the amplification of a selected sequence should be selected from sequences that are highly specific to WRN (and not, e.g., the Bloom's Syndrome gene, supra) and form stable duplexes with the target sequence. The primers should also be non-complementary, especially at the 3' end, should not form dimers with themselves or other primers, and should not form secondary structures or duplexes with other regions of DNA. In general, primers of about 18 to 20 nucleotides are preferred, and can be easily synthesized using techniques well known in the art. PCR products, and other nucleic acid amplification products, may be quantitated using techniques known in the art (Duplaa et al., Anal. Biochem. 212:229-236, 1993; Higuchi et al., Bio/Technology 11:1026-1030).

Within one embodiment of the invention, nucleic acid diagnostics may be developed which are capable of detecting the presence of Werner's Syndrome, or of various related diseases that may be caused by Werner's Syndrome. Briefly, severe mutations in the WRN gene may lead to Werner's Syndrome, as well as a host of related diseases, including for example, increased frequency of some benign and malignant neoplasms (especially sarcomas), cataracts, cardiovascular disease, osteoporosis, type I

aderage. In addition, many of the related diseases may be associated with mutations in

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the WRN gene. For example, diabetes and osteoporosis are often associated with aging. Aging population and individuals with these (or other) diseases are screened for mutations in WRN. Any of the assays described herein may be used. RT-PCR is especially preferred in conjunction with DNA sequence determination. To correlate a mutation or polymorphism with disease, sibling pairs in which one sibling has disease are preferred subjects. Once a mutation is identified, other convenient screening assays may be used to assay particular nucleotide changes.

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Since the sequences of the two copies of the gene from non-Werner's affected individuals can be correlated with the medical histories of these patients to define these correspondences, these alleles can therefore be used as diagnostics for susceptibilities to these diseases, once the relationship is defined. Certain non-null forms of the gene, for example, in either the homozygous or heterozygous state may significantly affect the propensity for the carriers to develop, for example, cancer. These propensities can be ascertained by examining the sequences of the gene (both copies) in a statistically significant sample of cancer patients. Other diseases (see above) can be similarly examined for significant correlations with certain alleles. To detect such a causal relationship one can use a chi-squared test, or other statistical test, to examine the significance of any correlation between the appropriate genotypes and the disease state as recorded in the medical records, using standard good practices of medical epidemiology. The sequences that define each of the alleles are then valuable diagnostic indicators for an increased susceptibility to the disease. Thus, from the nucleic acid sequences provided herein, a wide variety of Werner's Syndrome-related diseases may be readily detected.

Another cellular phenotype of the cells from Werner's patients is the increased frequency of deletion mutation in these cells. Clearly, the defective helicase in these cells leads to a specific mutator phenotype, while not rendering the cells hypersensitive to a variety of chemical or physical mutagens that damage DNA, like

some alietes may therefore be diagnostic of this class of medical conditions.

Assays for agonists and antagonists

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Also provided by the present invention are agonists or antagonists of the WRN gene product comprising a protein, peptide, chemical, or peptidomimetic that binds to the WRN gene product or interacts with a protein that binds to the WRN gene product such that the binding of the agonist or antagonist affects the activity of the WRN gene product. An agonist will activate or increase the activity of the WRN gene product. An antagonist will inhibit or decrease the activity of the WRN gene product. The activity of the WRN gene product may be measured in an assay, such as a helicase assay or other assay that measures an activity of the WRN gene product. Other assays measure the binding of protein that interacts with WRN and is necessary for its activity.

Agonists and antagonists of the WRN gene product may be used to enhance activity or inhibit activity of the gene product. Such agonists and antagonists may be identified by a variety of methods. For example, proteins that bind and activate WRN may be identified using a yeast 2 hybrid detection system. In this system, the WRN gene is fused to either a DNA-binding domain or an activating domain of a yeast gene such as GAL4. A cDNA library is constructed in a vector such that the inserts are fused to one of the domains. The vectors are co-transfected into yeast and selected for transcriptional activation of a reporter gene (Fields and Song, *Nature 340*: 245, 1989). The protein(s) that bind to WRN are candidate agonists. Three different proteins that bind WRN have been identified in an initial screen using the 2-hybrid system.

When the binding site on WRN gene product is determined, molecules that bind and activate WRN protein can be designed and evaluated. For example, computer modeling of the binding site can be generated and mimetics that bind can be designed. Antibodies to the binding site may be generated and analogues of native binding proteins generated as well. Any of these molecules is tested for agonist or antagonist activity by a functional assay of the WRN gene product. For example, to test

administered and activation is monitored. An antagonist will inhibit the activation of

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the reporter gene by at least 50%. Similarly, agonist activity may be measured by either enhancing WRN activity in a yeast 2-hybrid system or by coupling the test compound to a DNA binding or activation domain and monitoring activity of the reporter gene.

5 <u>Labels</u>

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WRN proteins, nucleic acid molecules which encodes such proteins, anti-WRN protein antibodies and agonists or antagonists, as described above and below, may be labeled with a variety of molecules, including for example, fluorescent molecules, toxins, and radionuclides. Representative examples of fluorescent molecules include fluorescein, *Phycobili* proteins, such as phycoerythrin, rhodamine. Texas red and luciferase. Representative examples of toxins include ricin, abrin diphtheria toxin, cholera toxin, gelonin, pokeweed antiviral protein, tritin, *Shigella* toxin, and *Pseudomonas* exotoxin A. Representative examples of radionuclides include Cu-64, Ga-67, Ga-68, Zr-89, Ru-97, Tc-99m, Rh-105, Pd-109, In-111, I-123, I-125, I-131, Re-186, Re-188, Au-198, Au-199, Pb-203, At-211, Pb-212 and Bi-212. In addition, the antibodies described above may also be labeled or conjugated to one partner of a ligand binding pair. Representative examples include avidin-biotin, and riboflavin-riboflavin binding protein.

Methods for conjugating or labeling the WRN proteins, nucleic acid molecules which encode such proteins, anti-WRN protein antibodies and agonists or antagonists, as discussed above, with the representative labels set forth above may be readily accomplished by one of ordinary skill in the art (see Trichothecene Antibody Conjugate, U.S. Patent No. 4,744,981,; Antibody Conjugate, U.S. Patent No. 5,106,951; Fluorogenic Materials and Labeling Techniques, U.S. Patent No. 4,018,884; Metal Radionuclide Labeled Proteins for Diagnosis and Therapy, U.S. Patent No. 4,897,255; and Metal Radionuclide Chelating Compounds for Improved Chelation Kinetics, U.S. Patent No. 4,988,496; see also Inman, Methods In Enzymoiosy. Vol. 34, 4 filinity

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Bioanalytical Applications," Anal Biochem 171:1-32, 1988).

Pharmaceutical Compositions

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As noted above, the present invention also provides a variety of pharmaceutical compositions, comprising one of the above-described WRN proteins, nucleic acid molecules, vectors, antibodies, host cells, agonists or antagonists, along with a pharmaceutically or physiologically acceptable carrier, excipients or diluents. Generally, such carriers should be nontoxic to recipients at the dosages and concentrations employed. Ordinarily, the preparation of such compositions entails combining the therapeutic agent with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with nonspecific serum albumin are exemplary appropriate diluents.

In addition, the pharmaceutical compositions of the present invention may be prepared for administration by a variety of different routes. In addition, pharmaceutical compositions of the present invention may be placed within containers, along with packaging material which provides instructions regarding the use of such pharmaceutical compositions. Generally, such instructions will include a tangible expression describing the reagent concentration, as well as within certain embodiments, relative amounts of excipient ingredients or diluents (e.g., water, saline or PBS) which may be necessary to reconstitute the pharmaceutical composition.

Methods of Treating or Preventing Werner's Syndrome

The present invention also provides methods for treating or preventing Werner's Syndrome (or related diseases), comprising the step of administering to a patient a vector (e.g., expression vector, viral vector, or viral particle containing a vector) or nucleic acid molecules alone, as described above, thereby reducing the

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may be used to delay onset of Werner's Syndrome, lessen symptoms, or hast or delay

progression of the disease. Such therapeutics may be tested in a transgenic animal model that expresses mutant protein, wild-type and mutant protein, or in an *in vitro* assay system (e.g., a helicase assay such as that described by Bjornson et al., *Biochem.* 3307:14306-14316, 1994).

As noted above, the present invention provides methods for treating or preventing Werner's Syndrome through the administration to a patient of a therapeutically effective amount of an antagonist or pharmaceutical composition as described herein. Such patients may be identified through clinical diagnosis based on the classical symptoms of Werner's Syndrome.

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As will be evident to one of skill in the art, the amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth. Typically, the compositions may be administered by a variety of techniques, as noted above.

Within other embodiments of the invention, the vectors which contain or express the nucleic acid molecules which encode the WRN proteins described above, or even the nucleic acid molecules themselves may be administered by a variety of alternative techniques, including for example administration of asialoosomucoid (ASOR) conjugated with poly-L-lysine DNA complexes (Cristano et al., *PNAS* 92122-92126, 1993), DNA linked to killed adenovirus (Curiel et al., *Hum. Gene Ther.* 3(2):147-154, 1992), cytofectin-mediated introduction (DMRIE-DOPE, Vical, Calif.), direct DNA injection (Acsadi et al., *Nature 352*:815-818, 1991); DNA ligand (Wu et al., *J. of Biol. Chem. 264*:16985-16987, 1989); lipofection (Felgner et al., *Proc. Natl. Acad. Sci. USA 84*:7413-7417, 1989); liposomes (Pickering et al., *Circ. 89*(1):13-21, 1994; and Wang et al., *PNAS 84*:7851-7855, 1987); microprojectile bombardment (Williams et al., *PNAS 88*:2726-2730, 1991); and direct delivery of nucleic acids which encode the WRN protein itself either alone (Vile and Hart. *Cancer Res.* 53: 3860-3864, 1993), or

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The following examples are offered by way of illustration, and not by way of limitation.

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EXAMPLES

EXAMPLE 1

CLONING OF THE WRN GENE FROM CHROMOSOME 8

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The WS locus (WRN) was initially localized to 8p12 by conventional mapping methods (Goto et al., Nature 355:735-738, 1992) and the genetic position refined using both meiotic and homozygosity mapping (Schellenberg et al., 1992; Nakura, et al., Genomics 23:600-608, 1994; Thomas, Genomics 16:685-690, 1993). The latter approach is possible since many WS subjects are the offspring of consanguineous marriages (Table 1). Initial mapping work (Nakura, et al., Genomics 23:600-608, 1994; Oshima et al., Genomics 23:100-113, 1994) placed the WRN locus in an 8.3 cM interval flanked by D8S137 and D8S87 (Fig. 1). D8S339, a marker within this interval, was the closest locus tested (q = 0.001, $Z_{max} = 15.93$). Multipoint analysis placed WRN within 0.6 cM of D8S339, although the region between D8S87 and FGFR could not be excluded. Subsequently, the short tandem repeat polymorphism (STRP) markers at glutathione reductase (GSR) and D8S339 were found to be in linkage disequilibrium with WS in Japanese WS subjects (Yu, American Journal of Human Genetics 55:356-364, 1994).

To clone the WRN gene, a yeast artificial chromosome (YAC) P1, and cosmid contig was generated starting at the *GSR/D8S339* region and extended by walking methods to cover approximately 3 Mb. An additional 16 STRP markers in the YAC contig (Fig. 1B) were identified to define recombinants and to delineate the boundaries of the linkage disequilibrium region. For marker ordering and gene identification, cosmids and P1 clones were also isolated and used to construct a small-clone partial contig of the region (Fig. 1E). The WRN region was defined by obligate

recombinants at C41C3S3 excluding the region telomeric to this marker, and at 9896R9

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Genes in the WRN region were identified by exon trapping using vector pSL3 (Buckler et al., Proc. Natl. Acad. Sci. USA 88:4005-4009, 1991; Church et al., Nat. Genet. 6:98-105, 1994), hybridization of cDNA libraries to immobilized YACs (Parimoo et al., Proc. Natl. Acad. Sci USA 87:3166-3169, 1991), and comparison of the genomic sequence to DNA sequence databases using BLAST (Altschul et al. J. Mol. Biol. 215:403-410, 1990) and the exon-finding program GRAIL (Uberbacher and Mural, Proc. Natl. Acad. Sci. USA 88:1261, 1991). The genomic sequence was determined for the region defined by P1 clones 2233, 2253, 3833, 2236, 2237, 2932, 6738 and 2934 and cosmid clone 176 C6. Each method identifies short segments of 10 expressed sequences, which were then used to screen an arrayed fibroblast cDNA library to identify longer cDNA clones. This library was selected because WS fibroblasts have a premature senescence phenotype in vitro, indicating that the WRN gene is probably expressed in this cell type. Genes identified by this process were screened for WRN mutations using reverse transcriptase-polymerase chain reaction (RT-PCR). Seven subjects were initially screened for mutations: 5 WRN subjects (2 Caucasians and 3 Japanese) and 2 control subjects (1 Caucasian and 1 Japanese). Prior to identification of the WRN gene, the following genes from the region were screened for mutations; GSR, PP2AB, TFIIEB, and genes corresponding to other expressed sequence tagged sites (ESTs).

The candidate WRN locus gene was initially detected by using the genomic sequence of P1 clone 2934 to search the EST database. A single 245 bp EST, R58879, was detected which is homologous to 3 segments of the genomic sequence separated by presumed intronic sequence. Sequence from R58879 was used to identify longer cDNA clones from a normal fibroblast cDNA library. An initial 2.1 kb cDNA clone containing EST R58879, which corresponds to the 3' end of the gene, was obtained by screening an array of clones by PCR, using the primers A and B (see below). Primers A and B are derived from R58879 sequence and yield a 145 bp clones were identified. An additional 8 clones were obtained by plaque hybridization. The longest clone is 4.0 kb in length. Additional sequence was obtained by the RAGE method using primer 5EA to prime first strand cDNA synthesis. A 2.5 kb product was obtained that contained an additional 1.4 kb of sequence.

Evidence that R58879 is expressed was obtained by Northern blot analysis, in which 6.5 kb and 8 kb transcripts were detected in a variety of tissues, including heart, placenta, muscle, and pancreas. Also, transcripts were detected by RT-PCR products from fibroblast and lymphoblastoid cell line RNA.

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EXAMPLE 2

CLONING OF THE WRN GENE FROM SUBJECTS

The WRN gene may be isolated from patients and mutations or polymorphisms determined by sequence analysis. Peripheral blood cells are obtained by venipuncture and hypotonic lysis of erythrocytes. DNA or RNA is isolated from these cells and the WRN gene isolated by amplification. The gene sequence may be obtained by amplification of the exons from genomic DNA or by RT-PCR, followed by determination of the DNA sequence. Primers suitable for determining the DNA sequence and for performing RT-PCR are listed below (Primers A-R arc SEQ ID Nos. 1-18 respectively, and primers 5EA-5EG are SEQ ID Nos. 19-25 respectively). Two cDNAs were identified and arc shown in Figures 2 and 3. There is some uncertainty regarding the identity of a few bases in the 5' untranslated region in Figure 2.

Two RT-PCR reactions are used to obtain the gene from different tissues. First strand cDNA synthesis is carried out according to standard procedures (e.g., with a Stratascript Kit from Stratagene). The cDNA is subjected to a pair of nested PCR amplifications, the first with primers I and J (SEQ ID Nos. 9 and 10), followed by primers K and L (SEQ ID Nos. 11 and 12), and the second with primers

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the gene sequence or splicing pattern. Primers A-H (SEQ ID Nos. 1-8)and K-R (SEQ

ID Nos. 11-18) are used for sequencing the first RT-PCR fragment. Primers B, 5EA, 5EB, 5EC, 5EE, 5EF and 5EG (SEQ ID Nos. 2, 19, 20, 21, 23, 24, and 25, repectively) are used for sequencing the second RT-PCR fragment. Sequencing is done on an ABI373A using Applied Biosystems Division of Perkin-Elmer FS sequencing kits according to the instructions of the manufacturer.

Α 5'-CTGGCAAGGATCAAACAGAGAG В 5'-CTTTATGAAGCCAATTTCTACCC C 5'-TGGCAAATTGGTAGAAGCTAGG 10 D 5'-AAATAACTATGCTTTCTTACATTTAC F 5'-CTCCCGTCAACTCAGATATGAG F 5'-CTGTTTGTAAATGTAAGAAAGCATAG 5'-GAGCTATGATGACACCACTGC G H 5'-ACTGAGCAACAGAGTGAGACC 15 5'-GGATCTGGTCTCACTCTGTTGC I J 5'-TTGCCTAGTGCAATTGGTCTCC K 5'-AGTGCAGTGGTGTCATCATAGC L 51-CCTATTTAATGGCACCCAAAATGC 5'-CAGTCTATGGCCATCACATACTC 20 N 5"-ACCGCTTGGGATAAGTGCATGC 0 5'-GAGAAGAAGTCTAACTTGGAGAAG Ρ 5 - TTCTGGTGACTGTACCATGATAC 0 5'-CCAAAGGAAGTGATACCAGCAAG R 5'-ACAGCAAGAAACATAATTGTTCTGG 25 5EA 5'-GAACTITGAAGTCCATCACGACC 5EB 5'-GCATTAATAAAGCTGACATTCGCC 5EC 5'-CATTACGGTGCTCCTAAGGACATG 5ED 5'-GATGGATTTGAAGATGGAGTAGAAG 5EE E' TGAAAGACAATATGGAAAGAGCTTG 30 5EF 5'-GTAGAACCAACTCATTCTAAATGCT 5EG 5 - AATTIGOGIGICATOOTIGOGCA

The exons of the 3'-end of the WRN gene can be amplified from DNA samples using the primers listed below (Primers E1A-E13B are SEQ ID Nos. 26-57, respectively). The DNA sequence is determined using the same primers and an ABISTS and ABISTS are sequenced.

	E1B	5'-CATGAAACTTGCTTCTAGGACAC
	E2A	51-CCCAGGAGTTCGAGACCATCC
	E2B	51-TTACAATCGGCCACATTCATCAC
	E2C	51-TGTAATCCCAACACTTTGGGAGG
5	E2D	51-AGTGGAAGAATTCATAGTGGATGG
	ЕЗА	5 - TAGCTTTATGAAGCCAATTTCTACC
	E3B	51-AATCCAAAGAATCAATAGACAAGTC
	E3C	5 GCTTGAAGGATGAGGCTCTGAG
	E3D	ET - TGTTCAGAATGAGCACGATGGG
10	E4A	51-CTTGTGAGAGGCCTATAAACTGG
	E4B	5'-GGTAAACAGTGTAGGAGTCTGC
	E5A	5 GCCATTTTC1CTTTAATTGGAAAGG
	E5B	5'-ATCTTATTCATCTTTCTGAGAATGG
	E6A	TGAAATAGCCCAACATCTGACAG
15	E6B	∵-GATTAATTTGACAGCTTGATTAGGC
	E7A	E1-TGAAATATAAACTCAGACTCTTAGC
	E7B	5'-GTACTGATTTGGAAAGACATTCTC
	E8A	5'-GATGTGACAGTGGAAGCTATGG
	E8B	5' GGAAAAATGIGGTATCTGAAGCTC
20	E9A	5'-AAGTGAGCAAATGTTGCTTCTGG
	E9B	5 TCATTAGGAAGCTGAACATCAGC
	E10A	5'-GTTGGAGGAAATTGATCCCMGTC
	E10B	5'-TGTTGCTTATGGGTTTAACTTGTG
	EllA	5'-TAAAGGATTAATGCTGTTAACAGTG
25	E11B	5'-TCACACTGAGCATTTACTACCTG
	E12A	5' GTAATCATATCAGAATTCATAACAG
	E12B	5'-CTTTGGCAACCTTCCACCTTCC
	E12C	5 - GCAAAGGAAATGTAGCACATAGAG
	E12D	5'-AGGCTATAGGCATTTGAAAGAGG
30	£13A	5'-GTAGGCTCCCAGAAGACCCAG
	E13B	5'-GAAAGGATGGGTGTGTATTCAGG

EXAMPLE 3

IDENTIFICATION OF MUTANT ALLELES

The cDNA sequence (Figure 2) was aligned to the genomic sequence to

codons in the open reading frame of the gene. In the fifth patient, a single base pair

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change results in a cysteine to arginine transition, which may disrupt gene function. Each of the exons was also sequenced in 96 unaffected control individuals (48 Caucasians and 48 Japanese), and none of the mutations were found in any of the control individuals.

The first mutation is a mutation at a splice acceptor site. In the sequence below, the GGTAGAAA sequence begins at nucleotide 2030 (Figure 2). The g to c change results in a deletion of 95 bp.

Preparation of DNA for RT-PCR mutational analysis revealed that for one subject, the amplification product was shorter than observed in products from other WS and control subjects. DNA sequence analysis of the RT-PCR product revealed that 95 bp were missing compared to other samples. The missing sequence corresponds to a single exon. This exon and flanking genomic segments were sequenced from the WS subject and controls and a single base change (G \rightarrow C) at the splice donor site was detected. The subject was the offspring of a first cousin marriage and was, as expected, homozygous for this mutation. The same mutation was found in a total of 18 out of 30 Japanese WS subjects and, thus, is the most common Japanese WS mutation. Deletion of this exon results in a change in the predicted open-reading frame and a premature stop codon. This mutation was not observed in 46 Japanese and 46 Caucasian controls. Among mutation carriers, 12/16 had the 141 bp allele at the GSR2-STRP.

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wild type: ttttaatagGGTAGAAA (SEQ ID No. 58)
Werners: ttttaatagGGTAGAAA (SEO ID No. 59)

The second mutation changes a C to T at nucleotide 2384 (Figure 2) changing a glutamine to a stop codon, which results in a predicted truncated protein. This mutation was observed in a single subject. Primers E11A and E11B flank this sequence and amplify a 360 bp fragment.

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The third mutation changes a C to T at nucleotide 2804 (Figure 2), which alters an arginine codon to a stop codon resulting in a predicted truncated protein. Four Japanese WS subjects and 1 Caucasian W5 subject had this mutation. Primers E8A and E8B flank this sequence and amplify a 267 bp product.

wild type: TTGGAGCGAGCA (SEQ ID No. 62)
Werners: TTGGAGTGAGCA (SEQ ID No. 63)
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The fourth mutation is a 4 bp deletion across a splice junction. The exon sequence shown below begins at nucleotide 2579 (Figure 2). This mutation was identified in a Syrian W5 kindred. Primers E4A and E4B flank this mutation and amplify a 267 bp fragment.

wild type: ctgtagACAGACACCTC (SEQ ID No. 68)
Werners: ctgt----AGACACCTC (SEQ ID No. 69)

The fifth mutation is a missense mutation. A T is altered to a G at nucleotide 2113 (Figure 2), changing the wild-type phe codon to a leu codon. This change is a polymorphism with each allele present at a frequency of approximately 0.5. It does not appear to correlate with WS.

phe
wild type: AAGAAGTTTCTTCTG
Werners: AAGAAGTTGCTTCTG
leu

(SEQ ID No. 64)
(SEQ ID No. 65)

The sixth mutation is a missense mutation changing of the action

Wind type: TTUATGTGAI (SEQ ID No. 66)
Werners: COTTCACGTGAT (SEQ ID No. 67)

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arg

These point mutations may also be identified by PCR using primers that contain as the 3'-most base either the wild type or the mutant nucleotide. Two separate reactions are performed using one of these primers and a common second primer. Amplification is detectable in the reaction containing a matched primer.

EXAMPLE 4

CHARACTERIZATION OF THE WRN GENE AND GENE PRODUCT

The 2 kb WRN cDNA hybridizes to a 6.5 kb RNA and a less abundant 8 kb RNA on a Northern blot, suggesting that a full length coding region is about 5.2 kb long. An overlapping cDNA clone has been isolated that extends the sequence by 2 kb. The insert from this clone is used to probe cDNA libraries to identify other clones that contain the 5' end of the cDNA or full length sequence. Alternate splicing events are detected by sequencing the full cDNA sequence from a number of different tissues, including fully differentiated cells and stem cells, and the full range of gene transcripts identified by sequence comparison. Additional exons are identified as above by further genomic sequencing and GRAIL analysis.

The predicted amino acid sequence is shown in Figures 2B and 3. Figure 2 shows cDNA and predicted amino acid sequences of the WRN gene. Figure 3 presents cDNA and predicted amino acid sequences of a less abundant transcript of the WRN gene. The longest open reading frame is shown from the first methionine in that frame. The predicted WRN protein consists of 1,432 amino acids divided into three regions: an N-terminal region, a central region containing 7 motifs (I, Ia, II, III, IV, V and VI) characteristic of the DNA and RNA superfamily of helicases (Gorbalenya et al. Nucleus 1 vid Rev. 17, 1713, 1989), and a Characteristic of the DNA and RNA superfamily of helicases (Gorbalenya et al.

Because many helicases function as part of a multiprotein complex, the N-terminal

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and/or the C-terminal domain may contain interaction sites for these other proteins, while the central helicase domain functions in the actual enzymatic unwinding of DNA or RNA duplexes.

The N-terminal region, encompassing approximately codons 1 to 539, is acidic; there are 109 aspartate or glutamate residues, including a stretch of 14 acidic residues in a 19 amino acid sequence (codons 507-526). Stretches of acidic residues are found in the Xeroderma pigmentosum (XP) complementation group B helicase, the Bloom's syndrome helicase, and the X-chromosome-linked α-thalassemia mental retardation syndrome helicase. In the WRN gene, this region also contains a tandem duplication of 27 amino acids in which each copy is encoded by a single exon. Because this duplication is exact at the nucleotide level, and because flanking intronic sequences for the two exons that encode the duplication are also highly similar, this duplication is presumed to be the result of a relatively recent event. The duplicated regions are also highly acidic with 8 glutamate or aspartate residues out of 27 amino acids and only 2 basic amino acids (one histidine and one lysine residue).

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The central region of the WRN gene, spanning approximately codons 540-963, is highly homologous to other helicases from a wide range of organisms including the ReqQ gene from *E. coli*, the SGS1 gene from *S. cerevisiae*, a predicted helicase (F18C5C) from *C. elegans*, and several human helicases. Thus, by sequence similarity, the WRN gene is a member of a superfamily of DExH-box DNA and RNA helicases. The principle conserved sequences consist of 7 motifs found in other helicases. These motifs include a predicted nucleotide binding site (motif I) and a Mg²¹ binding site (sequence DEAH, motif II). Some or all of the 7 motifs are presumed to form the enzymatic active site for DNA/RNA unwinding. The presence of the DEAH sequence and an ATP-binding motif further suggests that the WRN gene product is a functional helicase.

The C-terminal end of the WRN gene, from codons 964 to 1432, has

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EXAMPLE 5

IDENTIFYING AND DETECTING MUTATIONS IN THE WRN GENE

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Mutations or polymorphisms of WRN may be identified by various methods, including sequence analysis. Although any cell (other than erythrocytes) may be used to isolate nucleic acids, peripheral blood mononuclear ceils (PBMC) are Peripheral blood mononuclear cells are obtained by venipuncture and preferred. subsequent hypotonic lysis of crythrocytes. RNA is isolated and first strand cDNA synthesis is performed using a Strata-script RT-PCR kit according to the manufacturers instructions (Stratagene, La Jolla, part numbers 200347 and 200420). Three RT-PCR fragments are amplified using an LA PCR Kit Ver. 2 using buffer containing 1.5 mM Mg+2 (TaKaRa Shuzo Co., Ltd., Japan, part number RR013A). Nested PCR is performed. In this reaction, a second PCR is performed using a pair of primers within the sequence amplified by the first PCR reaction. The cycling conditions for each amplification are: 10 min at 95°C, 35 cycles of 1 min at 60°C, 1 min at 72°C, and 1 min at 95°C, followed by 7 min at 72°C in a Perkin-Elmer 9600 PCR machine. The amplified fragments are purified using 96-well plate spin columns (Wang et al., Anal. Biochem. 226:85-90, 1995). DNA sequence is determined using an FS Dye-Terminator sequencing kit (Applied Biosystems Division of Perkin Elmer) and the specific primers described below. An automated Applied Biosystems ABI373A DNA Sequencer is used to determine the sequence. The amplified fragments and the appropriate primers are listed in Table 1, and the primer sequences are listed in Table 2.

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The DNA sequences are aligned with the known sequence (Figure 2A) using the program Sequencher (Gene Codes, Michigan) to identify any discrepancies between patient samples and the reference sequence.

Table 1 PCR and sequence primers

Fragment	Primers Nested on cDNA		Coordinates	Sequence primers
	1st PCR	2nd PCR		,
I	5EC, J	5EN, L	2947-5065	5EN. L, M, N, O, P, Q, R
II	5ED, P	5EE, B	1379-3391	5EE, 5EJ, 5EK, 5EL, 5EM, 5EB, 5EA, 5EN, B
111	5ES, 5EK	5ET, 5EH	75-1516	5ET, 5EX, 5E1, 5EP, 5EO, 5ED, 5EH

Table 2 Primer sequences

5		Table 2 Primer sequences	
2	_		
	Б	5'-CTTTATGAAGCCAATTTCTACCC	(SEQ ID No. 2)
	J	5'-TTGCCTAGTGCAATTGGTCTCC	(SEQ ID No. 10)
	L	5'-CCTATTTAATGGCACCCAAAATGC	(SEQ ID No. 12)
	М	5'-CAGTCTATGGCCATCACATACTC	(SEQ ID No. 13)
10	N	5'-ACCGCTTGGGATAAGTGCATGC	(SEQ ID No. 14)
	0	5'-GAGAAGAAGTCTAACTTGGAGAAG	(SEQ ID No. 15)
	P	5 '-TTCTGGTGACTGTACCATGATAC	(SEQ ID No. 16)
	Q	5 '-CCAAAGGAAGTGATACCAGCAAG	(SEQ ID No. 17)
	R	5 '-ACAGCAAGAAACATAATTGTTCTGG	(SEQ ID No. 18)
15	5EA	5'-GAACTTTGAAGTCCATCACGACC	(SEQ ID No. 19)
	5EB	5'-GCATTAATAAAGCTGACATTCGCC	(SEQ ID No. 20)
	5EC	5'-CATTACGGTGCTCCTAAGGACATG	(SEQ ID No. 21)
	5ED	5 ' - GATGGATTTGAAGATGGAGTAGAAG	(SEQ ID No. 22)
	5EE	5'-TGAAAGAGAATATGGAAAGAGCTTG	(SEQ ID No. 23)
20	5EH	5'-CATTGGGAGATAAATGCTCAGTAGA	(SEQ ID No. 80)
	5EJ	5'-AGATGTACTTTGGCCATTCCAG	(SEQ ID No. 81)
	5EK	5'-GCCATGACAGCAACATTATCTC	(SEQ ID No. 82)
	5EL	5'-CTTACTGCTACTGCAAGTTCTTC	(SEQ ID No. 83)
	5EM	5'-TOGATCAAAAOCAGTACAGGTG	(SEQ ID No. 84)
25	5EN	5'-GCAGATGTAGGAGACAAATCATC	(SEQ ID No. 85)
	5EO	5'-TCATCCAAAATCTCTAAATTTCGG	(SEQ ID No. 86)
	5EP	5'-CTGAGGACCAGAAACTGTATGC	(SEQ ID No. 87)
	5ES	5'-GCTGATTTGGTGTCTAGCCTGG	(SEQ ID No. 88)
	5ET	5'-TGCCTGGGTTGCAGGCCTGC	(SEQ ID No. 89)
30	5EX	5'-TTGGAAACAACTGCACAGCAGC	(SEQ ID No. 90)

EXAMPLF 6

ISOLATION OF GENOMIC DNA CONTAINING WERNER'S SYNDROME GENE

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To facilitate mutational analysis of the WRN gene, the intron-exon structure is determined. The WRN gene is located in the genomic sequence of P1 clone 2934. However, this clone only contains the 3' end of the gene (exons 21 to 35). Genomic clones containing the 5' end are obtained from a chromosome 8-specific cosmid library LA08NC01 (Wood et al. Cytogenet. Cell Genet. 59: 243, 1992) by screening for clones adjacent to P1 clone 2934. Briefly, this library is arrayed for PCR screening as described in Amemiya et al. (Nucl. Acids Res. 20: 2559, 1992). WRN containing cosmids are identified using primer sets 5E6/5EY, 5ED/5E12, and CD-A/CD-B (Table 3), which are derived from the WRN cDNA sequence (Figure 1; GenBank Accession No. L76937). Four walking steps yielded cosmids 193B5. 114D2, 78D8 and 194C3, which contained the remaining exons. Primers derived from the WRN cDNA were used for the initial sequence analysis of the cosmid clones. The resulting sequence (Figure 5) is compared to the cDNA sequence to identify intron-exon boundaries. Sequencing primers are then designed from the intron sequences to obtain sequence in the reverse direction and to obtain the second boundary defining the intronexon junction. This strategy is used to define the exons not present in P1 clone 2934.

Table 3. Primer sequence and PCR conditions for WRN analysis

Region	Primer Sequence	Product Size (bp)	Mg+2 (mM)	рH
N-domain	5E6 51-GATATTGTTTTGTATTTACCCATG4AGAC (SEC IC No. 184 5EY 51-TCCGCTGCTGTGCAGTTGTTTCC SEQ ID No. 165)	166	1.5	8 3
er e	ing second transport of the control	***		

The annealing temperature was 60° C for all primer sets.

Table 4 presents a summary of the structure of the genomic WRN gene.

The first column identifies the exon, the second column indicates the base numbers of the cDNA that are derived from the exon, the third column denotes the size of the exon in bp, the fourth column shows the sequence of the boundaries with intron sequences in lower case letters and exon sequences in upper case letters, the fifth column shows notable features of the exons.

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Table 4. Intron-Exon Structure of the WRN Gene

Exon	cĐNA Location	Exon Size (bp)	Intron-Exon Boundary Sequences	Exon Features
1	1-155	>155	TTCTCGGGgtaaagtgtc (SEO ID No. 169)	5°UTR
2	156-327	1/2	tacctctcagTTTTCTTTAAAGAAAGgtatgttgtt (SEQ ID No. 170)	5'UTR, ATG codon
3	328-440	113	taaactcaagGCATGTGTGATATTAGgtaagtgatt (SEQ ID No. 171)	
4	441-586	146	<pre>ctcactttagCATGAGTCCATGTCAGgttggtatct (SEQ ID No. 172)</pre>	
5	587-735	149	aatgttacagTTTTTCCC ATAAAAAGgtaaaagcaa (SEO ID No. 173)	
É	736-885	150	toatttctagCTGAAATG ATGCTTATqtacqtnott (SEO ID No. 174)	
7	886-955	70	fiffitatagGCTGGTTT AAATAAAGgtatgttaag (SEQ ID No. 175)	
8	956-1070	115	ttccccctaqAGGAAGAACCACGGAGgttaaatatt (SEQ ID No. 176)	
9	1071 - 1500	430	ttttttttagGGTTTCTACTACTGAGqtactaaaat (SEO ID No. 177)	
10	1501 -	81	tfttttaaaqCATTTATC == TGCTTAAGaqtatqt***	ong Transformación
·	.563 1807	148	esaptiticadiulii(AsA - ISATAA sedtaadiesii) Es£3 ID No. 180	

Exon	cONA Location	Exon Size (bp)	Intron-Exch Boundary Sequences	Exon Features
13	1808 - 1883	76	ttatttccagACTTTTTGTTTAAACCgtgagtataa (SEQ ID No. 181)	
14	1884 - 1951	68	<pre>caccttcaagAGTTCAGTGGCAACTGqtaaqttgta (SEQ ID No 182)</pre>	helicase motif ((5) end)
15	1952 - 2060	109	t.catttcaagGATATGGACAGCTTAAgtaagtcatg (SEQ ID No. 183)	helicase motif [(3' end) and [a
16	2061 - 2129	69	cttcttatagAATGTCCAAFTAAATTgtgagtaatt (SEQ ID No. 184)	
17	2130 - 2212	83	gtttttacagAGGTAMAT TGATATTGgtaagtgala (SEQ ID No. 186)	
18	2213- 2319	10/	<pre>ttttttacagGTATCACGTGCCAATGqtaagcttig (SEO ID No. 186)</pre>	helicase motif II
19	2320 - 2504	185	<pre>catcattcagGTTCCAATAAAACAAGgtaaggattt (SEQ ID No. 187)</pre>	helicase motif III
20	2505- 2679	175	ttttctttagTTCCCACTAAATTCAGgtatgaggat (SEQ 1D No. 188)	nelicase motif IV
21	2680- 2861	182	ttgttctcagTGTGTCAT. ITAAATAGgtadaadaad (SEQ ID No. 189)	helicase motifs V and VI
22	2962 - 2963	102	taatcgacagGCACCTTCAGGAGACAgtatgtatta (SEQ ID No. 190)	
23	1964 3056	93	tottgggtagAATCATCTAGGTCCAGgtaaagattt (SEQ ID No. 191)	
24	3057 - 3198	14?	ftttatttagATTGGATCGAGGATCTgtaagtatat (SEQ ID No. 192)	
25	3199 - 3369	171	<pre>ctaatttcagAATTCTCA</pre>	
26	?370- !464	95	crittaaragGGTAGAAA (CTGCCTAGgttmattfft) SEG ID No. 194)	
27	:465- 3540	76	tittttttagTTCGAAAA . AGAAGAAGgtttgtttta (SEQ ID Nc. 198)	
28	3541 - 3614	74	ttaaatgcagTCTAACTT / AAAAAAAGgtacagagtt (SEO ID No. 196)	
29	3615- 3690	76	aatattttagTATCATGG AGACTCAGgtaaggcttt	

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f. xon	cDNA Location	Exon Size (bp)	Intron-Exon Boundary Sequences	Exch Features
32	3919- 4050	132	eattctgtagACAGACCTTGCCTTTGgtaagtgtga (SEQ ID No. 200)	
33	4051 - 4213	163	ctttctctagAAGAGCATCAACTCAGgtgagaggca (SEQ ID No. 201)	
34	4214 - 4422	209	tcgtttacagATATGAGTATACTGAGgtattaatta (SEQ ID No. 202)	
35	4423 - 5190	768	tttcctacagACTTCATC (SEO ID No. 203)	TAA codon.3'UTR

Note. Exons are in uppercase and intron sequences are in lowercase letters.

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As shown above, WRN contains a total of 35 exons ranging in size from 68 bp (exon 14) to 768 bp (exon 35). The coding region begins in the second exon (Table 2). As noted previously, there is a duplicated region in the WRN cDNA sequence which is 27 amino acids in length. This duplication is exactly conserved at the nucleotide level in cDNA. At the genomic level, the duplicated sequences were present as 2 exons (exons 10 and 11), each exon containing only the duplicated nucleotides. The intronic sequences adjacent to these 2 exons are also highly conserved, suggesting that the a relatively recent duplication event is responsible for these repeated exons. In addition, because the surrounding intronic sequences were conserved, it was not possible to design primers which could specifically amplify exons 10 and 11.

The helicase region of the WRN gene is contained in exons 14-21. Helicase motif 1 is split between exons 14 and 15 while the remaining motifs are each in an individual exon (Table 4). This region, from codon 569 to 859, has sequence similarity to the 7 signature helicase motifs. In addition, though the sequences between the motifs are not conserved, the spacing is very similar in genes from a wide range of species. For example, the helicase domains in the *E. coli RecQ* gene are found in a

EXAMPLE 7

IDENTIFICATION OF MUTATIONS

Initially, 4 different mutations in the C-terminal domain of WRN were identified. These mutations accounted for more than 80% of the Japanese WS patients examined. All 4 mutations are in the C-terminal domain region of WRN and the resulting predicted protein contained an intact helicase domain. Additional WS subjects are screened to identify further mutations. Genomic structure information is used to design PCR-primers for amplifying each exon, which is then subjected to DNA sequence analysis. Five additional WRN mutations are described; 2 are located in the consensus helicase motifs and another 2 are predicted to produce truncated proteins without the helicase domains. These mutations suggest that in at least some WS subjects, the enzymatic helicase activity is destroyed and support that complete loss-of-function of WRN gene product causes Werner's syndrome.

Although any cell may be used to isolate DNA, PBMC are preferred. As 15 above. PBMC are obtained by venipuncture and subsequent hypotonic lysis of erythrocytes. PBMC are lysed by the addition of detergent, such as 0.5% NP-40, 0.5% Triton-X100, or 0.5% SDS. If a non-ionic detergent is used, no further purification of DNA is necessary, but proteinase K treatment, and subsequent heat killing of the enzyme (95°C for 10 minutes) is required. Genomic DNA is amplified according to the PCR conditions recited above using the primers listed in Table 5. Exons 9 and 10 are 20 contained in a region of DNA that is duplicated. The primer pair for exon 9 and 10 anneals to sequences outside the duplication. Amplified product is analyzed by DNA sequence determination, hybridization with allele-specific probe, or other mutation detection method. When DNA sequences are determined, the sequence of the amplified exon is aligned with the known sequence (Figure 2A) and any discrepancies between 25 patient samples and the reference sequence are identified.

Table 5

PCR Fragment	Primer Sequence	Product Size (bp)	Mg*2 (mM)	рН
exon l	A 5'-AGGGCCTCCACGCATGACGC (SEQ ID No. 92) B 5'-AGTCTGTTTTCCAGAATCTCCC (SEQ ID No. 93)	583	1.5	8.3
exon 2	A 5'-CCTATGCTTGGACCTAGGTGTC (SEQ ID No. 94) B 5'-GAAGTTTACAAGTAACAACTGACTC (SEQ ID No. 95)	339	1.5	8.3
exon 3	A 5'-ACTATAAATTGAATGCTTCAGTGAAC (SEC ID No. 96) B 5'-GAACACACCTCACCTGTAAAACTC (SEQ ID No. 97)	316	1.5	8.3
exon 4	E 5'-GGTAAACCACCATACCTGGCC (GEO ID No. 98) F 5'-GTACATATCCTGGTCATTTAGCC (GEO ID No. 99)	691	1.5	8.3
exon 5	B 5'-ATTCAGATAGAAAGTACATTCTGTG (SEQ ID No 100) E 5'-GTTAAGAAATACTCAAGGTCAATGTG (SEQ ID No. 101)	369	1.5	8.3
exon 6	A 51-GGTTGTATTTTGGTATAACATTTCC (SEQ ID No. 102) 8 51-ATATTTTGGTAGAGTTTCTGCCAC (SEQ ID No. 103)	374	1.5	8 3
exon 7	A 51-CTCTTCGATTTTCTGAAGAYGGG (SEQ 1D No. 104) E 51-CCCTAATAGTCAGGAGTGTTCAG (SEQ 1D No. 105)	291	: 5	<u>a</u> 3
exon 8	A 51-GGAAAGAAAATTTGATCCC (SEQ ID No. 106) B 51-CAGCCTTAATGAATAGTATTCTTCAC (SEQ ID No. 107)	316	4.0	8 3
exon 9	C 51-ATTGATETTTTAAGTGAAGGTCAGC	668) C.	ā .

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PCR Fragment	Primer Sequence	Product Size (bp)	Mg ⁻² (mM)	рН
	(SEQ ID No. 111)			
exon 13	A 51-TAACCCATGGTAGCTGTCACTG (GEG_ID_No112) B 51-CTGTTGCTGTTAAGCAGACAGG (GEO_ID_No113)	285	1.5	8.3
exon 14	C 5'-TTGAATGGGACATTGGTCAAATGG (SEQ ID No. 114) F 5'-GTAGTTGCAFTTGTATTTTGAGAGT (SEQ ID No. 115)	348	1 5	8.3
exon 15	C 51-GTAAAAAGAAATGAAAGCATCAAAGG 12EQ ID No. 116) D 51-TCACCCACAGAAGAAAAAAAGAGG (SEQ ID No. 117)	246	4.0	8 3
exon 16	A 51 CAAAAAAGAAAATTGCAAAGAACAGG (DEQ ID No. 118) 8 51-CAGCAACATGTAATTCACCCACG (SEQ ID No. 119)	282	4.0	8.3
exon 17	S GAAGAGACTGGAATTGGGTTTGG (SEQ ID No. 120) 5 -ATAGAGTATCATGGGATAAGATAGG (SEQ ID No. 121)	532	1.5	8 3
exon 18	A 51-TICTCCTTTGGAGATGTAGATGAG (GEQ ID No. 122) B 51-TCTTCAGCTTCTTTACCAGTCCCCA (CEQ ID No. 123)	273	4 0	10
exon 19	A 51-CATGGTGTTTGACAACAGGATGG (1E3 ID No. 124) H 51-GTTAAATATGCATTAGAAGGAAATCU (1E0 ID No. 125)	396	4)	9.0
exon 20	A 51-ATAAAACCAAACGGGTOTGAAGO (JEO ID No. 126) B 51-AAAAGAAGTATTCAATAAAGATCTGG (SEQ ID No. 127)	342	4 0	8.3
exon 21	A 51-AATTCCACTTTGTGCCAGGGACT (SEQ ID No. 128) R 51-ACTTGGGATACTCCAAATACCCT	397	1 €	9.6

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PCR Fragment	Primer Sequence	Product Size (bp)	Mg ⁻² (mM)	pН
exon 23	A 5'-CTGAAGTCAAATAATGAAGTCCCA (SEO ID No. 132) B 5'-GTTTGCTTTCTCATATCTAAACACA (SEO ID No. 133)	360	4 (8.3
exon 24	A 51-CTTGTGAGAGGCCTATAAACTGG (SEQ ID No. 134) B 51-GGTAAACAGTGTAGGAGTCTGC (SEQ ID No. 135)	267	<u>:</u> 5	8.3
exon 25	C 51-GCTTG/AGGATGAGGCTCTGAG (SEQ ID NG. 136) D 51-TGTTCAGAATGAGCACGATGGG (SEQ ID No. 137)	461	1.5	8 3
exon 26	A 51-CTTGTGAGAGGCCTATAAACTGG (SEQ ID No. 138) B 51-GGTAAACAGTGTAGGAGTCTGC (SEQ ID No. 139)	267	1.6	8.3
exon 27	A 5'-GCCATTTCTCTTTAATTGGAAAGG (SEQ ID No. 140) B 5'-ATCTTATTCATCTTTCTGAGAATGG (SEQ ID No. 141)	274	1.5	8.3
exon 28	A 5'-TGAAATAGCCCAACATCTGACAG (SEQ ID No. 142) B 5'-GATTAATTGACAGCTTGATTAGGC (SEQ ID No. 143)	291	1.5	8.3
exon 29	A 51-TGAAATATAAACTCAGACTCTTAGC GEQ ID No. 144: E-51-GTACTGATTTGGAAAGACATTCTC GEQ ID No. 145:	303	1.5	8.3
exan 30	A 5 -GATGTGACAGTGGAAGCTATGG (SEC ID No. 146) B 5'-GGAAAAATGTGGTATCTGAAGCTC (SEO ID No. 147)	307	1 5	8-3
exon 3:	A 51-AAGTGAGCAAATGTTGCTTCTGG (SEG ID No. 148) 5-51-TCATTAGGAAGCTGAACATCAGC	304	1 6	8 3

ETTO NO. 18.1

PCR Fragment	Primer Sequence	Product Size (bp)	Mg ⁻² (m M)	рН
exon 33	A 5'-TAAAGGATTAATGCTGTTAACAGTG (SEQ ID No. 152) B 5'-TCACACTGAGCATTTACTACCTG (SEQ ID No. 153)	360	1 5	8.3
exon 34	C 5' GCAAAGGAAATGTAGCACATAGAG (SEQ ID No 154) D 5'-AGGCTATAGGCATTTGAAAGAGG (SEQ ID No 155)	491	1.5	8.3
exon 35	A 51-GTAGGCTCCCAGAAGACCCAG (SEQ ID No. 156) B 51-GAAAGGATGGGTGTATTCAGG (SEQ ID No. 157)	406	1.5	8 3
mutation 7	GD A 51-ACAGGCCATAGTTTGCCAACCC (SEQ ID No. 158) GD D 51-IGGTATTAGAATTTCCCTTTCTTCC (SEQ ID No. 159)	426 2002	1.5	9.0 8.3
DJG RT-PCR	SEE 5'-TGAAAGAGAATATGGAAAGAGGCTTG (SEQ 1D No. 160) E S'-CTTTATGAAGCCAATITCTACCC (SEQ 1D No. 161)		2.0	8 3
P2934AT1	A 51-TCAAAATCAGTCGCCTCATCCC (SEO ID No. 162) B 51-CAATGTATCAGTCAGGGTTCACC (SEO ID No. 163)	168	2.0	03

The annealing temperature was 60° C for all primer sets.

reverse strand

Mutations are detected by amplifying WRN exons from genomic DNA and directly cycle-sequencing the PCR products by dye-terminator cycle sequencing (Perkin Elmer) and an ABI373 automated DNA sequencer. Prior to sequencing, the PCR-amplified exon fragments were purified using a QIAquick 8 PCR purification kit (Qiagen). The resulting sequences are aligned by FASTA analysis (GCG). Nucleotide differences between WS and controls are subsequently confirmed by sequencing the 10

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consequences of splice-junction mutations. RT-PCR products were synthesized from

mRNA isolated from lymphoblastoid cell lines (Qiagen Oligotex, Qiagen). The large genomic deletion was detected in genomic DNA using long-range PCR (Expand Long Template PCR System, Boehringer Mannheim).

Diagnostic Criteria. WS patients were from an International Registry of Werner's Syndrome subjects. Diagnostic criteria are based on the following signs and symptoms (Nakura et al. 1994). Cardinal signs are: 1) bilateral cataracts; 2) characteristic dermatological pathology (tight skin, atrophic skin, pigmentary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy) and characteristic facies ("bird" facies); 3) short stature; 4) paternal consanguinity (3rd cousin or greater) or affected sibling; 5) premature greying and/or thinning of scalp hair: 6) positive 24hour urinary hyaluronic acid test, when available). Further criteria are: 1) diabetes mellitus; 2) hypogonadism (secondary sexual underdevelopment, diminished fertility, testicular or ovarian atrophy); 3) osteoporosis; 4) osteosclerosis of distal phalanges of fingers and/or toes (X-ray diagnosis); 5) soft tissue calcification; 6) evidence of premature atherosclerosis (e.g. history of myocardial infarction); 7) mesenchymal neoplasms, rare neoplasms or multiple neoplasms; 8) voice changes (high pitched, squeaky or hoarse voice); 9) flat feet. Diagnostic classifications are as follows: "Definite", all cardinal signs (#6 when available) and any 2 others; "Probable", the first 3 cardinal signs and any 2 others; "Possible", either cataracts or dermatological alterations and any 4 others; "Excluded", onset of signs and symptoms before adolescence (except short stature since current data on pre-adolescent growth patterns is inadequate) or a negative hyaluronic acid test. Family designations are as previously used (Nakura et al. 1994; Goddard et al. 1996; Yu et al. 1996).

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Mutations in WS Subjects. Initial screening of the WRN gene was based on sequence from only the 3' end of the gene (exons 23-35). Thus the first 4 mutations (designated 1-4, Table 3) were in the region 3' to the helicase domains. In this mutation screening, primers amplify exons 2-35 along with approximately 80 bp of

screened for mutations. These subjects were selected based on haplotype analysis that

suggested that each subject might have a different mutation (Yu et al. 1994; Goddard et al. 1996). A total of 30 Japanese and 36 Caucasian subjects were ultimately screened for each mutation by DNA sequence analysis of the appropriate exon.

Table 6. Summary of WRN Mutations

Mutation	Codon	Exon	Type of Mutation	Nucleotide Sequence	Comment	Predicted Protein Length
none						1432
1	1165	30	substitution	CAG (Gln) to <u>T</u> AG (terminator)	попуснус	1164
2	1305	33	substitution	CGA (Arg) to <u>T</u> GA (terminator)	nonsense	1034
3	1230	32	4 bp deletion	gt <u>ag-AC</u> AG to gt- AG	4 bp deletion at splice-donor site	1247
4	1047- 1078	24	substitution	tag-GGT to tac-GGT	substitution at splice-donor site	1060
5	369	9	substitution	CGA (Arg) to <u>T</u> GA (terminator)	nonsense	368
6	889	22	substitution	CGA (Arg) to <u>T</u> GA (terminator)	nonsense	888
7	759- 8 16	20	substitution	CAG-gta to CAG-tta	substitution at splice-receptor site	760
8	389	9	1 bp deletion	AGAG (Arg) to GAG (Glu)	frame-shift	391
9	697- 942	19- 23	deletion (> 15 kb)	-	genomic deletion	1186

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Table 7. Mutation Status of WS Subjects¹

Mutation	Japanese WS Subjects		Non-Japanese WS Subjects		
	Homozygous	Heterozygous	Homozygous	Heterozygous	
1	SYD				
2	HH ^D , HM ^D , MH ^M ,		GAR ^o		
3			SYR ¹		
4	FJ ^D , FUW ^D , HA ¹ , HW ^D , IU ^D , JO1 ^D , JO2 ^D , KAKU ^D , KY ^D , MCI ^D , MIE2 ¹ , SK ^D , ST ^D , TH ¹ , TK ^M , TO ^D , ZM ^D , 78-85 ¹ .				
5	KO ^D , OW ^P	KUN'	EKL ^D . AG0780 ^I , AG4103 ^M	DJG ^P , CP3 [‡] , NF ^M	
6			CTA ^D	SUGIP	
7	WKH ^D				
8				FES'	
9				DJG ^P , SUG1 ^P	

Diagnosis categories: Definite; Probable; Possible; Insufficient data. The country of origin (ethnic group) of non-Japanese subjects are: AG00780, USA (Caucasian); AG04103, USA (Caucasian); CTA. England (India, East African, Asian); CP3, France (Caucasian); DJG, Germany (German), EKL. Switzer; and (German); FES, Germany (German); NF, France (Caucasian); SUG, USA (Caucasian); SYR. Syria (Syrian). AG04103 and AG00780 were obtained as cell lines from the Aging Cell Repository (Camden, New Jersey).

Five new WS mutations were detected in the WRN gene (designated 5-9.

Table 6). Two of the mutations (5 and 6) were single base substitutions creating

nonsense codons. Mutation 5 results in a C-T transition changing an Arg to a

caucasian subjects were homozygous, and 1 Japanese and 4 Caucasians were heterozygous for this mutation (Table 7). Mutation 6 is also a $C \rightarrow T$ transition changing

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an Arg to a nonsense codon. One Caucasian WS subject was homozygous for this mutation, and a second was a compound heterozygote. The predicted protein product is 888 amino acids. A third substitution mutation (mutation 7) was a G→T change at a splice-receptor site, generating a truncated mRNA devoid of exon 20 and a prematurely terminated WRN protein at amino acid 760. A single Japanese WS subject was homozygous for this mutation.

Two deletions were observed. One (mutation 8) is a 1 bp deletion at codon 389 resulting in a frame shift and a predicted truncated protein 391 amino acids long. This mutation is found in one Caucasian patient as a heterozygote. The second (mutation 9) is a much larger deletion. This deletion was first observed in RT-PCR experiments when 2 different RT-PCR products were obtained from RNA prepared from subject DJG. RT-PCR products produced by primers 5EE and B (Table 5) yielded 2 different products, one with the expected size of 2009 bp, and a second, shorter product approximately 700 bp smaller. The DNA sequence of the shorter product revealed that exons 19 through 23 were missing. To further establish the nature of this mutation, primers (exon 18A and exon 24A, Table 5) derived from the exons flanking this potential gross deletion (exons 18 and 24) were used to amplify genomic DNA from subject DJG using a long-range PCR protocol. A single 5 kb fragment was observed corresponding to the shorter RT-PCR product. (The normal fragment, which is estimated to be > 20 kb was not observed.) The complete DNA sequence of this 5 kb fragment was determined and contained the expected 3' and 5' ends of exons 18 and 24. respectively. The exonic sequences were separated by intronic sequences adjacent to the 3' and 5' end of exons 18 and 24, respectively. No sequences from exons 19-23 were found in the 5 kb fragment. In other subjects and controls, the intronic sequence in the intron 3' to exon 18 contained 531 bp of unique sequence followed by a 241 bp Alu repeat element. Likewise, for the region 5' to exon 24, there is an Alu repeat element separated from exon 24 by 3,460 bp of unique sequence. The 4938 bp

recombination error at 2 highly homologous Alu elements within the WRN gene. A

primer set, GD-A and GD-D (Table 5) was designed to specifically amplify a short fragment (426 bp) across this junction point. A single additional Caucasian WS patient, SUG, was shown to contain this genomic deletion. Further PCR amplification of the exons within this deleted region demonstrated that both DJG and SUG are heterozygous for this mutation.

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Origins of WRN Mutations. Because multiple subjects have the same mutation and because the same mutation was observed in different ethnic groups, at least some of the mutations likely originated in common founders. Evidence for a common founder was examined using 2 short tandem repeat polymorphisms (STRPs) within the WRN gene. These STRPs, D8S2162 and p2934AT1, were isolated from the same P1 clone (p2934) and are within 17.5 kb of each other. While D8S2162 is not particularly polymorphic (heterozygosity = 54% in Japanese and 70% in Caucasians) and is primarily a 2 allele system (140 and 142 bp alleles), p2934AT1 is highly polymorphic (heterozygosity = 78% in both Japanese and Caucasian populations). For mutation 4, which has only been observed in Japanese subjects, all but 1 subject had the D8S2164/p2934AT1 haplotype of 140-148 (Table 8). The single exception. JO2, has the haplotype 140-150, with the p2934AT1 allele being 2 bp different from the 148 bp allele observed in other subjects with mutation 4. This 2 bp difference may be the result of a 2bp mutation, as is commonly observed in dinucleotide repeat STRP loci (Weber and Wong, 1993). The haplotype data is consistent with a common Japanese founder and is consistent with the linkage disequilibrium observed in the same Japanese subjects for other markers in the WRN region (Yu et al. 1994; Goddard et al., 1996). For mutations 2 and 5, in the Japanese, the 896R18-p2934AT1 haplotypes for the small number of available subjects, are consistent with common founders for each mutation. However, the non-Japanese subjects with mutations 2 and 5 have discordant p2934AT1 genotypes when compared to Japanese subjects with the same mutations. These results do not support a common founder for both Japanese and non-Japanese subjects with

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discordant for p2934AT1 (e.g. compare AG00780 to EKL). It should be noted that

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absence of evidence for a common founder does not necessarily exclude the possibility of a single originating mutational event. Intragenic recombination and/or mutations creating new alleles at the 2 STRP loci could, over time, obscure the origins of the different WRN mutations.

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Table 8. STRP Genotypes at the WRN gene¹.

Subject	Ethnic Group	Mutation	y896r18	p2934at1
FJ. FUW, HA, HW, JO1, KAKU, KY, MIE2, TO	Japanese	4	140/140	148/148
JO2	Japanese	4	140/140	150/150
HM, MH, NN,	Japanese	2	140/140	144/144
GAR	Hispanic	2	140/140	156/156
OW, KO	Japanese	5	140/140	148/148
AG00780	Caucasian	5	142/142	136/136
EKL, AG04103	Caucasian	5	142/142	128/128
CP3	Caucasian	5/?	142/150	128/142
KUN	Japanese	5/?	140/142	128/148
DJG	Caucasian	5/9	140/142	128/del ²

¹Genotype data for HH, SK, ST, TH, TK, and ZM was not available For y896R18, alleles in bp (frequency for Caucasians, frequency for Japanese) were as follows: 136 (0.030, 0.025); 138 (0.020, 0.010); 140 (0.460, 0.576); 142 (0.337, 0.359); 144 (0.084, 0.010); 146 (0, 0.010); 148 (0.009, 0.010); 150 (0.059, 0). For p2934AT1, alleles in bp (Caucasian frequency, Japanese frequency) were as follows: 114 (0.006, 0): 122 (0, 0.009); 124 (0.011, 0); 128 (0.253, 0.079); 130 (0, 0.018); 132 (0.006, 0.009); 134 (0.046, 0.096); 136 (0.086, 0.009); 138 (0.011, 0); 140 (0.034, 0); 142 (0.052, 0.035); 144 (0.023, 0.061); 146 (0.023, 0.053); 148 (0.034, 0.132); 150 (0.034, 0.105); 152 (0.057, 0.123); 154 (0.063, 0.088); 156 (0.086, 0.070); 158 (0.098, 0.070); 160 (0.046, 0.018); 162 (0.029, 0.009); 166 (0, 0.009); 168 (0, 0.009).

The 5 mutations identified here demonstrate that WS mutations are not restricted to the 3' end of the gene, but are also found in other regions of WRN. In addition, mutations 5 and 7-9 each disrupt either part or all of the helicase region. Thus the WS subjects homozygous for this mutation will completely lack the WRN helicase

proparty results in complete loss of all activity of the WRN protein. However, the WS phenotype in these subjects is not appreciably distinct from the WS phenotype

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generated by the other mutations described here. Thus, all mutations in the WS gene may be complete loss of function mutations.

PCT/US96/20785

EXAMPLE 8

IDENTIFICATION OF MOUSE WRN GENE

The mouse WRN cDNA was isolated by screening a mouse splenocyte cDNA library at low strengency with human WRN cDNA as probe. The mouse cDNA sequence is presented in Figure 9. The homology between human and mouse WRN cDNA sequence is about 80%. On the amino acid level, the human and mouse WRN gene product show about 90% identity. Notably, the repeated exon in human WRN cDNA (exons 10 and 11) is only present once in mouse WRN cDNA.

Genomic mouse WRN clone was isolated by using mouse WRN specific primers to screen mouse genomic BAC library. The genomic DNA sequence is presented in Figure 6.

The genomic DNA sequence is presented in Figure 7 and SEQ ID NOS: 207-209. The DNA sequence is presented in Figure 6 and SEQ ID NOS: 205 and 206.

EXAMPLE 9

LOCALIZATION OF THE WRN GENE PRODUCT

A rabbit polyclonal antiserum raised to a peptide of WRN gene product is used in an indirect immunofluorescence assay to determine the intracellular localization of the WRN protein.

A rabbit polyclonal antiserum is raised to the peptide Phe-Pro-Gly-Ser-Glu-Glu-Ile-Cys-Ser-Ser-Ser-Lys-Arg (FPGSEEICSSSKR) (SEQ ID NO: 204) by standard methods (see Harlow and Lane, Antibodies, A Laboratory Manual, CSH Press, Cold Spring Harbor, 1989; Current Protocols in Immunology, Greene Publishing, 1995). The peptide corresponds to residues 1375 through 1387 of the WRN

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0.5% Triton X-100. 10 mM PIPES, pH 6.8, 50 mM NaCl, 300 mM sucrose, and 3 mM MgCl₂ (see for example, Fey et al., J. Biol. Chem. 98: 1973, 1984). The cells are then stained for 20 min with a suitable dilution of the anti-peptide antibody (1:1500), washed, stained with a suitable second antibody (e.g., FITC-conjugated goat anti-rabbit antibody), washed, and mounted for visualization by gluorescence microscopy. Control stains include bis-benzimidine (Sigma, St. Louis, MO), which stains DNA, and phalloidin (Molecular Probes, OR, BODIPY 558/568 phalloidin), which stains filamentous actin.

As seen in Figure 9, the WRN gene product is almost entirely located in the nucleus. Nuclear staining is readily noted in the epithelial cells at the bottom left in panel A. These cells are close to the periphery of the expanding clone of human prostate epithelial cells. Cells that are not rapidly dividing (e.g., cells closer to the center of the clone), such as those seen in the upper right of panel A, are stained in both the cytoplasm and nucleus. The location and size of the nuclei in these cells is shown by staining DNA with the intercalating dye bis-benzimidine (Hoeschst 33258), panel B. The overall size of the cells and in some cases key cytoskeletal features are revealed by staining for F-actin as shown in panel C.

EXAMPLE 10

ISOLATION OF A PROTEIN THAT BINDS TO THE WRN GENE PRODUCT

A yeast 2-hybrid interaction screen (Hollenberg et al., *Mol. Cell Biol. 13*: 3813, 1995) is used to identify and isolate a cellular protein that binds to the carboxy-terminal 443 amino acids (residues 990 through 1432) of the WRN gene product.

A library of 1.1 x 106 independent cDNA clones generated from RNA isolated from stimulated human peripheral blood mononuclear cells is generated in pACT-2 (Clontech, Palo Alto, CA) that creates cDNA/GAL4 activation domain fusions is co-transfected into yeast containing pLEXA with the WRN gene fragment to generate

for nistidine. 6" colonies grew on this medium. Of these, 60 were cured of the pLFXA

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plasmid by growth on medium containing cycloheximide and mated with a yeast strain expressing a fusion of a "sticky" laminin and the GAL4 activation domain. 19 clones did not activate the sticky protein and underwent DNA sequence analysis. Of these, 6 contained sequences that did not match any sequence in GenBank by BLAST search. Two other clones encoded carnitine palmitoyl transferase I and prolyl 4-hydroxylase B subunit. Six independent clones encoded a 70K component of the U1 snRNP complex (GenBank Accession No. M22636). Moreover, all six derived from the RNA recognition motif region of the 70K protein.

From the foregoing, it will be appreciated that, although specific embodiments of this invention have been described herein for the pruposes of illustration, various modifications may be made without departing from the spirit and scope of the invention. Accordingly, the invention is not limited except by the appended claims.

Claims

We claim:

- 1. An isolated nucleic acid molecule encoding a WRN gene product.
- 2. An isolated nucleic acid molecule selected from the group consisting of:
- (a) an isolated nucleic acid molecule as set forth in the Figures or complementary sequence thereof;
- (b) an isolated nucleic acid molecule that specifically hybridizes to the nucleic acid molecule of (a) under conditions of high stringency; and
 - (c) an isolated nucleic acid that encodes a WRN gene product.
- 3. An expression vector, comprising a promoter operably linked to a nucleic acid molecule according to any one of claims 1 or 2.
- 4. The expression vector according to claim 3 wherein said promoter is selected from the group consisting of CMV I-E promoter, SV40 early promoter and MuLV LTR.
- 5. The expression vector according to claim 3 wherein said promoter is a tissue-specific promoter.
- 6. A viral vector capable of directing the expression of a nucleic acid molecule according to claims 1 or 2.
 - 7. The viral vector according to claim 6 wherein said vector is selected

- 8. A host cell carrying a vector according to any one of claims 3 to 7.
- 9. The host cell according to claim 8 wherein said cell is selected from the group consisting of human cell, dog cell, monkey cell, rat cell and mouse cell.
 - 10. An isolated protein comprising a WRN gene product.
- 11. An antibody which specifically binds to the protein according to claim 10.
- 12. The antibody according to claim 11 wherein said antibody is a monoclonal antibody.
- 13. The antibody according to claim 11 wherein said antibody is selected from the group consisting of an Fab fragment, an Fv fragment and a single chain antibody.
 - 14. A hybridoma capable of producing an antibody according to claim 12.
- 15. A nucleic acid probe which is capable of specifically hybridizing to a WRN gene under conditions of high stringency.
- 16. A pair of primers capable of specifically amplifying all or a portion of a nucleic acid molecule according to any one claims 1 or 2.
- 17. A transgenic animal whose germ cells and somatic cells contain a WRN gene which is operably linked to a promoter effective for the expression of said gene, said gene being introduced into said mouse, or an ancestor of said mouse, at an embryonic

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- 18. The transgenic animal according to claim 17 wherein the animal is selected from the group consisting of a mouse, a rat and a dog.
- 19. The transgenic animal according to claim 17 wherein WRN is expressed from a vector according to any one of claims 3 to 7.
 - 20. An agonist of a WRN gene product.
 - 21. An antagonist of a WRN gene product.

FIGURE 1

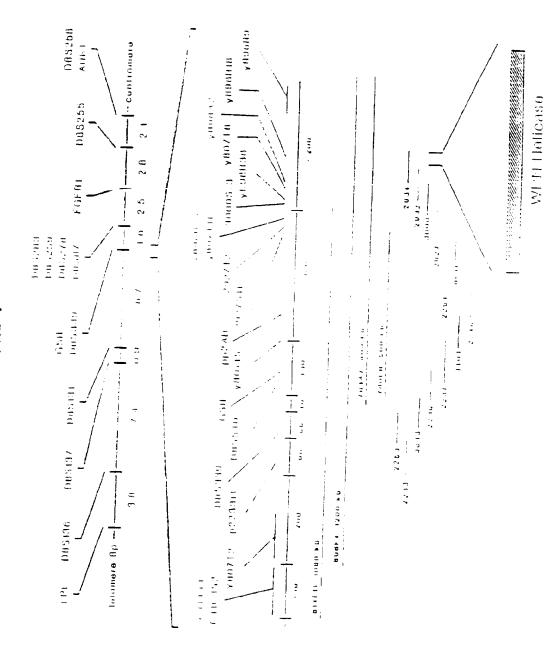


FIGURE 2A

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FIGURE 2B

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FIGURE 3C

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FIGURE 4A

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SSLAMER WKOVEGPHIL	FODE-DIASYAT TATTEFILES	12-27 helicases mat (recg ecoli, pro) 12-27 helicases mat (YAMC_SCHPO pro)
200		77 helicases.maf (Agein.12-27.12 pro)
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FIGURE AB

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FIGURE 5A

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			TOTTOTATOT	10127/2777	ACCTTENCY.	20,0
T.~455577733	TTTTTTTALLET	EATAITTINA	ATTTTAMAGA	ACAMETAC DALA	TTAKTTAGGT	11:0
	IATOTA-ATT	77.34347777	107710713.27	ACTIACTACI	777777777	1163
TRADATABAA	DATES CARA	1137111111	TTTTTACATA	3034777777		2023
CACACTTOTA	1070713400	TT TT TX T T X T	1732177344	7347777777	NOTACACACT	2223
1013.23.7011	SCTRTTMAT	ATGGAATATA	TT:\\\\C3T\\\		1000000000	23,3
ATTTTATTT	7073777777			377277777		
		TAMADOTACT	AGGACATTA	STATIONATE	733337777	1400
23,777,234,23	TTIATINATA	SATADIATTI		20070777.000	- 28787 777 3	2,50
AATCCTTATT	TELETIMENT	TTAACACCAA	ATRATAGTER	TTINATINA	37327722722	2511
27 22444 2 2 2 2	72277724477	TTGCGTRTig	4033577325		KTOOTOACSA	2533
NOTE DESCRIPTION	1733217744	TERRETARIA	NACH TTOX	SCARCCATT	10000000000	25-2
TOTATILITIE	TESTEACHE					
		FFT 577 573.3	AAAAAACTAG	**************************************	WIWHIE	:7::
	iii tactica	\$400715.2TT	307030344	77777133.27	TTATITTATI	1763
1037447757	ATTESTISASA	SAASAAASTT	2722337237	23727577	120111222	2311
	AATTIINIAA	7723737223	ACCOMMIST	CONSTRUCTO	11.777755757	1911
TAGITIRAAT	AUTOMASTE	2300077377	27.3.727777	TTTAKEASAS	AATAATTTST	2940
AGAGTAATIT	DESTRICTST'S	347077775	TODATTOTIA	ATSATTSCEN	TEARTOSTEE	1005
AGAATTTTTT	TAATTTTIA					
7077		PERSONAL PROPERTY.	TTTTTTT	0.40000000000	777777	3050
CCCNANASAN	AAATAAATAT	\$100 FT \$2.77.7	SCOSTTAASA	3773733777	7377773733	3127
₩77777777	CACACTERES	AGATTACTTA	₩TSTAJSTS	ATTTTEALITA	ATALIMATA	3 - 3 0
COATORADDA	SASTT TT SAA	GAGTITCIS:	ATTTTTTT			11.1
	STATASCASS	TORACOASST	DAAL WASA	AACAAAATAA	AU TANAMA	3320
₩ 27537777	TATTETTTCA					
		357454434	STOP ATTAC	AGTIGACTEE	2772727223	3265
777777		Participation of the Control of the	ROSKSSTSSA	WATITIAA	TAGAAAATTI	3425
	::≪****** <u></u>	ATTITIONATI	ASTSSTEEST	TTSASTASTS	TAATTAASTT	1480
7777777377	353,2777,577	3500T 10A 2T	T722777333	7537777	:=::::::::::::::::::::::::::::::::::::	35,3
7771177777	\$777577	1977737713	7535775773	EMUTATERES.	375375757	3613

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 	 * = = · ·	

FIGURE 5B

						4250
ATT. WENSAS	TENTEATER	TTATEGETTEE	ATT SACTOR	وببروا	ACTION	
TOTTATTIA	22277777	TAAATTTTAT	ATGGCAAACA	ARTERSTER S	*******	4320
73448844ET	TAXETTEXAE	ACTTSACTSS	TOTTETERINA	TAACTERTAA	されていれているか	4380
CASTITICA	2000270770	TEETSAAGAG	TTTATAGAGA	TAXAGGTTC:	WITTERSET.	1440
######################################	TTTTTTACTT	######################################	AGTITICITEAT	ACTANATANA	ATAMOMATA	4500
ACCETTERAC	735522223	TAMMATTAM	TAAATTSTAS	AACCATTOTT	75225544	456C
AAGTTTTTTA	2377777777	SAMATSAMA	ACCTTAGAGE	TTTT:		4623
		JACACAGGAA				463C
						4740
		************				480C
		TAMANAAA				4860
		CACAGGEAE				4920
		FATGGGAAAG				498C
						5040
		TATTTATGC				
		AATAATTATS				5100
		AGGCTAACTT				5150
		ATTAATGGTG				5220
TAACRTATRO	37777777	TTTTATTAA	TTTAMATTT	TSTSTTSSST	AGAATERTET	5 2 3 C
		CAAGTACAAA				3340
		TODAGGTAAA				5400
		TCATGTTT				5 + 5 =
		AATSTSTTTA				5520
						551:
		AGURATRARA				3 - 1
		TTANATATT				
		TACOTTOT:				5777
		NTTACATTC			3 AACTTTIGAT	:7::
		. 327272444				::1:
4747737372	ATTTAALACA	- 47 23777 773	: ::::::::::::::::::::::::::::::::::::	: STEASESTT:	: KOCACACAAA	1117
7300310377	TATATTATE	FOATATA TAT	- STATATATA	. ATATATETA	RIATATATET	13-1
4747374747					FIRIADADAD N	1111
TOASTOTATT					CASTTTONAL	8080
	::-:-			<u>-</u>	(: ::::::	6111
432277777					9 NOTOGATORA	5111
					T ATAMATTTES	42.
	and a contract of the contract	TACACCAAC				4333
					A HADAGTERS	6163
INTERTACE		: :ATC:ATA=:			A ROADATOATO	
					S GAGNAATAGA	5-123
					i wattakii	5 1 2 7
					a amagymatar	3340
TTEACETTT	TAGAGETT	: TACTIMACA			S TOCKSATECA	5522
STATTIATI	R ACRIIBATT.	NITATTERSAS	T DATAAAADA	A ACTITION A	A KTTTAASAAT	5555
CTTCTATTT	CATATTTT	T EASTROAFT	DAARTRAAC	T ASAAAASAA	T MENGANGE	5711
734233333					A AMERICATIAN	5730
					A ATTAMATAS	5347
					a maatace	6900
					N AGCAMCAMOS	5360
					A SAACATAAST	1020
					E ADADTDADA E	7030
					S STOAKTAGAA	7243
					a attacasa	7233
					W SACENTACE	7250
					A TEATMESSA	7000
						7331
					TAIDAADATT II	74.0
TAGACCEAT	T SAMITITAT	TINAMATI	T STEAMAT	A AATOOCOT	TAKEAAADDT DA	7:00
					AUTADOATKE DE	7540
					IA NONNADATI	7523
					SECEDIMENT OF	7531
13777755	J TSATASATT	7 4770772	T DATTTTA	:: 30ACTTAE.	AT DARTITATIE	17,0
					TA TOTTAATTIA	-300
						-111
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		 المحادات بالمتاه فتجيرا	:
1117713.71 777 2 1777	:	 . 15 n 1 k 1 0 1 n k	1. "
11:11:11:11:1:	314777777	 AAAAT AAT AA ITAAT NA A	3 .
	*	 	4.4

FIGURE 5C

323227755	T TORRECTERAC	ACT TOAGAA	taggettees		SACCOCATOT	3460
	~ ~~~~~~~~					3520
3~~~~~~	- numma - ma	~~~				3580
STIRTIST	A GOGTAAACAA	75051111			~~~~	
*********	70777777		10.404			3640
407474755			3.44.40.2	ta ctoatta a		a Too
22.722.22	A GCCTTAGAGC	AND CARCTAT	ASCASTOTAT	TT:::::::::::::	***********	3750
JAC	·				~ , ~~~~ ~~~	3820
	acue.noun.	TT0020TT1-				3380
	- ~~	200000000000000000000000000000000000000	1010			3940
	·	33555555			~~~~~~	3000
2000000	~ ~~~~~~~~					
TURNICUE	777774	11171700.0		JACTA-TT-1	Ju. Anich aun	3060
2000000		~~~~~	~	ATSTGGTGGS	SAGTGCTTTT	9110
	. ACTITICANO	JAGGCAGG	AGAATISTST	32700077	SCCSCACTTS	9130
	AGATESTSSS	VC.10CFC.	AGCTTSGGEA	ACAGAGCGAG	ACTOTOTOTO	924C
~~~~~~.	- ^^-	10.3000 3000	<u> </u>	3,0000000000000000000000000000000000000		9100
	•	AACT 3.75				91:0
		37.73.27.3.73.3				9420
UM M - NU C .	~-3~ - d - do					
GETTEENAG	DEACATEMET :		2030	~~		3+31
1772735454		177777777			•••	2552
	CAGILICAST		3557567777	2 <b>44</b> 070777	SCE <b>TENAT</b> ES	9611
			SCATTATAGG	COTTANGEDRA	CACTETTAC	9553
	J = . **** ***** *		353535555		-,	3700
J 7 J .				23,20000737	MASSETTAN	3731
NTACTT : 773		TRIBURALIT	STITTERA	SCTCTACTAC		3 3 - 3
	TTENATOAAT	772234				3321
TEASTTNESS	: STARATARS:	3237344	1244477777			
733227773	. ATRATTERTÁ		3.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7			3960
4407711000	734,271,23,77	14.73.72.71.75		TIAASTTAA		::::::
7737777287		Telle New London	~		\$70 2773 202	-1111
177777777		-was-2001_00		771222777	-ATTTTM::::	111.1
		ITTATORIOR	IGTOMAJĄJĄ	777144407337	1070111111	1:1::
ATTITIBAST	*********		~~~~~~~~~~~	7000000000	220122-025	11111
777827775	2778277722	1,000000000000	100111	ITTERRETTS	1040010143	11121
STTEEFFER	20003333777	3377337775		10034335310		12281
TOT TAXALAX	44 <b>44</b> 23-2444		111111111	ROTALACACOT	1013070577	
23,23,237,275	4000043000		TUACUATA			11441
TORACACOAS		ATTA-112.02.1				- 3 5 3 3
TANALAS ET				IAAAATTITA	AT-MCIA/CIA/	11111
TARTONTAAT			137100000	COCACTTAT		13611
		SHERITAT	TANGET LEETE	ACTAWAGACA	TTAGEAGAAT	111557
<b>₩</b> 1111450	3-5-1777	7000000444	\$778773737	ITTIMATATT	CAATTOMET	11741
<u> </u>	TT TALAK JA TA	277 327 27.42	3384833335		AGTTGAAGTT	
737327323.7		33 07 00 <del>11 11</del>	17727100	7327732573		11141
122 TTTATIA	TACTTT TACK	_	DOCTOR STEEL	1284777842		10311
4777304754	- RA 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		1371 \ -	10100TT 100		
773732353	JOATTTOOST		777377777 (c)			12311
AGAIN ITTEA	TTM3552A43		1000	A TAS INSETT		11111
STTANASASA			Au	AUTHORSTIA	TTTATTITIA	11111
7577777111	SATTOTOTOS	5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5. 5	TTACATA	₩CXCTTCT.	AAATT STEET	11151
·	ATTATIVATO	~~~~~	**********	1772~1243	STATTERAGE	11221
				AACRITITI	ACTATAAAGA	11111
	O			TTTTTTTACAG	AACCAATGCT	111,1
	ACCCATOTO	CATTONACTO				11,11
~~~~		433,47475				11,51
-01 - 0-3-MOV3	- ^~~~~	3-22773444.7	11-1-1			
TSCAACTAAA	TTGGAAGTTT	-	7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7			11111
TTTTTTTTTC	CASSITERAN			TTTTTTAGAG		11331
TTT 1333777	AAGICATTIT			3007000700	~	11543
3003003	2722773377					11711
						11763
		30.000				11:11
			——			11111
	~ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		–			
						1277
		-	111. 1 70. 1		*****	
40707777777		·				

FIGURE 5D

***********	TEEGGTATAA	TSAACTTTAT	TCATAGCTT	TEALECAST	TOCACATTT	11660
		ATTETTATES		SATTTTTIMA		12720
		TOTTATTATT			3073,777,023,7	12780
	CACCATACAT		TSSTCCACA			12340
		AATTTEGAAT				11900
		TTTTTTTTTAT				11960
		TGATTGTAAC				
						13020
		JTTAAACACT				1308C
TATOOCATOT		TENTSTTENA	JCTJATUTT	AGETETELAG	ರಾಯರಾಯ	13140
		ACATTECAT				13200
SATANTTAGS	*****	777727773	FCAAGGGACA	SSTAGAACAA	AATTOTCOTT	11260
TTTTTTTAGA	AASTATTAAA	TTTTTCLLCC	AAAACTTTAG	TTATAGGGAT	7.XT.T.T.T.X.X	13320
ATSTCTAATT	TENSTRACIA	TATTTTTTGGAC	ATATTTATTT	*********	TTSSTATSAG	73390
AAGTATTTAA	AGTTATAAGA	AAATTSTSST	************	ACTAATGAAT	AAATAATSAA	13440
TTAMETTERS		TTSGAGTSAT	TGATGTTCCL	37::77777777	AAACAACCAC	13500
COUTACAAAT	STEARTANER	TAGGACCETT	SCACTTENAG	AGCTTGTTCT	372077777	12560
COTTUNENTS	ATTTTTT	CTSATTTAGA	ACTOTATAAA	SCAAAGCTAA	STATTACACA	13520
CTSATAATSS	CTCAATAAAT	CAAGAGCIAG	AGATAGGATA	CTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	ATTECATATIO	13480
ATTAMMATE	TACTTTAAAA	TAGAGATTAA	AATTETESTA	TTEAATETAG	AATAGGTAAG	10740
3. 	TEXALTACTO	SAATSCTTCA	TOTANATACT	TTETENSTTT	374	13300
AAAGGAACAT			AATSGCGTGA			12360
	3877777777		Jettococok	7171771111		12320
	AAAAAAA.		AATTAGTTOT			11750
717772			TTENTOTTET			
**************************************	TETALATTA					1,0,1
52 573 7777			ACAMAL LINA		STTCCCTAAS	14111
		37722237777	5			150
103131771			AMATETATTE	101111111		1-11:
	TINITTIANI		TAAAATTAT			1,111
470000000	STITESTATI					1.143
1901/17/41				ATTAGAGTAG		53
357777777			. STUTKICHT	TOTOKAKATAT		14460
	\$4.4.000000000					
1771.4.4.1					TOSTESSATA	. → 5 5 1
	AATTATIITT		TEAGAATTTA	STSAAACSTT	122 7777 77, 22	14543
WELL STATES	- Natio athe	CTTTCTACAT	" JATTTT DAG D	TTTTAAATAA	NEXTTT AAS	14733
7 77772 44734	7722837773	CONDANATED	TAATITATAT	AAATATATA	LATAGTAGIA	14753
CONTACALT	27 27 27 7. C.	. IAASATTTT	TODAKTKOTK	TAAACACTTA	. 1513.00173.1	1-421
7733343777	TTOWATACKS	TTTAAAATTT			TATTAGAAAT	14880
TA4A33373A	. KOTTATTAGT					14340
122217777	WARRITTT	TATAMATAT			TTAATTTAT	13400
404771344					373244.7775	13 36 3
		. AATTITAAA		CACTAGRATI		19120
7770378473		CTATACACA				13130
					TAGACAANCT	13140
					7777227777	13300
37777	TACAATTAT				TOTACTTO	13353
3000000000	307777335	1077777111			AGCCCCCCCC	13420
		TTTMAXAT		·	ATTSAACTTA	13.480
33,377		: SCAGTSGTS				
		COTTAGETT			TTIAACTIT	15540
200000000000000000000000000000000000000						15500
					i icatittici	13553
			- JATACILA	i ancultius.	COALAGE	. 5 T2 C
	er de la composition de la composition La composition de la		~ ~~~		TATOGETATT	1 E T 3 C
			. J.A.A.GGC.		\	13343
			. CATOTATIA	: 30 22 37137	T ASTTANSANS	15303
***.TACTT	~~:3TX55X	J AJAATTACA	T AAGGGACST	A TEAATACAT	N TAMATUST S	15950
		· JTTTTAJA	J AAATTAGAJ;	; :::::::::::::::::::::::::::::::::::::	: AMITTATIAS	14010
1222 2771	TAITTIT ST	I GAATATATA	O TAGA TTI TO.	S TOTEATAGE	TESATTTESA	16030
1377232733	. IAJAASSIL	ACAACCAAAAA	A TOSTSGASA	A DAATIDIAT	T INCOUTACE.	1:140
	1723277777	N AGAMOTTAA	T ATTONOMAC	1 00004-000	T TT:TT:T:	18170
77777777	77777777	: :: :::::::::::	-			

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CONTROL OF THE STATE OF THE STA
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FIGURE 5E

SAGTTAAACT	ننت: تشند	TGACCTOTCC	72007-1-1-			15863
AGGATGAGC:						
AACATACAGT	TTTAAATTTS		4.5.00.072			16920
		:::::::::::::::::::::::::::::::::::::::	SKDETAKEEE	ATCCTACTT	ACKCCTTOTAX	15380
						17240
			0.000m			17120
			GCAGGTTSAG			
TAGGAATTES	. SGACTSCROT	222222	30000	1.1000000	-14144	-7150
ACCAATACCC		3400-4.34.	TACACCACTS	CACTOCAGES	CASACTOCET	17220
		SAATSAATSA	ATTAATTAAT	3247344734	ATTCCCCAART	17230
~.		AUCAUC.				17340
GGACAACTTA	23000.7730.7					
TONGANATOR	TWICKT		~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	40400CZ		17430
		3		TACTOTOTOT	T.XX TT CT ST TT	17463
					SGGAATATGA	17520
	ACAAAGATAC					1.290
SATCHTONS	SUANGGUNCA			~~~~~···	TATASTTATT	17540
~		20000	ACTOATCAGA	TAXAACTTES.		17730
		4	~~			17760
						17320
7723000000	JAAAGCCAAC	71.7171.771		JUNE CALLA	. AALAAU. J.	17330
********			37.03.0000		ATTANGANAT	17340
			TANTANA	2300	TTACAGAGC	13000
		A- 1100	~~ ~~ ~~ ~~ ~~			13257
TACTTOCATA		11171717		220101000	AAAA. 3AA	
7536573277	TAGETTAAGA	7		2-24040 <u>01</u> 4	. 460373667	19121
			STATSTATAT	TESSTETTE	TITTIGACCCC	13120
	3750775770			AAAAATTROO	3777377777	13740
3744733343		A - CTAGUEA	FIRECATOR	TERRESTERS		11111
CCAGTOTAGG		1040101450	7,000,000,444,44			
0000000000	AATATATA		~ ~ ~ ~ · · · · · · · · · · · · · · · ·	Table and a comment		13060
727777177	ATTENDEST				DAGDATOTTT	18410
** **			ATTATTATAT	STOTE CASTS	13.007771257	13491
TAINHAIAJA			NATTADA: 0	7327737777		. 3 5 • 3
7777327277	43 27777 277		3704345377			
TIAAJITITI	ATAATTTITI	AP DARTATE :			7724377	18601
00000000000	77 253 2 77 77		TTAAAAATOA	STRADATAGA	703443030	13443
		DAWLETTETAT	PATETTTTET	1773777732	TTATIONAL	13700
- NACTED ATT	ATTIKKATO	~~~37,77.23	477771	37775773	-:-::::::::::::::::::::::::::::::::::::	13730
DIAITKO			~		1237777777	
3777777777	124440000	TUNNATORE				13340
STTOTATES	7727447727				STRIKCTTON	13900
8777770807		1370171143	32122X122	TABASTTOTT	TATTTTACKT	11961
	TTTXXXCXTT	277,077,000	2342227146	7030007730	CACACACACT	13020
ACTTOTTAGE	44.3 5 77.3344.3	DEFICIAL	TT1.77-77-	3777A7377	TTTAATT	13240
TETTTTTATE	37377774	AVATATAATE				
	27377273 77	TENTETTEA	3.5300000	INAMATTIKT	TITTINGCIA	19145
AASTATASST	ATTAGAAGGT		an e i i kuluku		ACATTTTT	19100
			PTODAKTOTA	TAGGCACTCC	777777777	19252
777777777	real realist		7777377273		TOTONAMONT	13111
73 7777777	TACCITATI	TTTTTTTT				
AAD DATKEEN	3737773793			JAAATACTAG		13130
TTCTCXACA		TOTGATTET		AASTISTST\	2722222	13440
		STATITUTAL	ATTTATSTAT	37.3377.5775	772737777	19300
JAAJCETTST	~	TT:\\C.\\TT:	4445	RETAKTOR		19550
ATCAATTCAA	TAXXXXXXXXX	ACCUTTOTAL				
770770722	773	72777				12510
TAXACTTTEK	773651-1-1	TATTUTTULA	1:	334	<u> </u>	13500
-::::						19740
				STINIARTIA	777777777	19400
			77.00.73.77	TATAATATTS	TTGACAAGGT	12360
	~~ · ~~ · · · · · · ·		~~ ~ ~ ~ ~ ~ ~ ~ ~			
37 TAX TTT 10	32222		J. 334.	AASTATTT	JANGUENTET.	13313
7117117777	SAASSTTEEN SAASSTTEEN	******		2732377233	7.455.44.5575	13930
						00040
CACCADAGGA	TAGETTAS			3.05.00		10160
0003334300	7.5.3.77.1.1.1	77177	37327	. 3753 7 5313	373730302	20220
						20230

				* - * - *	•	•
				_		
5 5 5 5 5 5 5 5 F 5				* 1 - 1 - 1	47777 7 14271	. 1 15
1 4 4 1 20 10 10 1	\$2005 (Tipar)	1900-165	74 Tivelier			11311
7-1-47-17	11171717171			51555 FA 6		

FIGURE 5F

4077243333	TAXATTETA	AATSATTAAS	••••			
ACASTA		~~~~	TAAACTTTGC	4075747347	1TTCNAAAGC	21260
AGCTTTTTTTT			79%3 7.21. 5	EXCTSCACTS	LISSATSAA T	21123
			770777777		TAGATGGAGT	11130
		75ASTSEAST	SSCOTCATOR	2345721573	***********	21240
TT C C CAGA TT	: Exercenter	TOUTSOUTEN	CCTCCCCA	1ACCTSGSAC	22000000000	11100
COCCACACA	· ETTSSCT.Wit	**********		ACSGSSTTTS	ACEATOTTAG	11163
CONTOATEST						
SSATTACAGO			ATTTSSTTS:	************	CAACTICT!	21420
		TOCOTTOTAL		TOSTTOTAGE	7775335757	11480
465ATTTT			STEASTITES	TAAGAGGTCT	*******	11540
ADCTAAGTET			ATACACTOCC	CARTICATOR	CANTATATA	21400
TOAKATTTO	: tac ultu ltt	TANDACACAA	AAGGAACATT	ATTTTATAL	TOTATTATT	21560
TOTELGE	. 3737721322	TGAGCACGAT	JOSTATIACA	TTTTTTAG5	TTTTTAAGT	21.700
TORNATTEN	TOTANATORN	AAGAATTAAT	AGACAAGTET		TAACTTATAT	
37777.2.2.773	. GEATTITAS			323 7777 267		21730
SCEENTERN	_			770000	:::::::::::::::::::::::::::::::::::::::	11340
			20CYCLEGGY	AGGATEAAAS	ACAGAGTT 35	21900
7 3522 333777			JAGGGATTET	TEGTAGAAGT	TTOTOSTAT	21360
*ACCAMETET		7000 000 .300	AAAAAAATTAA	ACACTOTAGG	4077777777	12323
TTTSACTTA		EXCTERACKT	TANAMATATEE		TAATAGGGTA	22232
JAAATT 15.TT	TIATAMASTT	SATACACAA	TTENENGEST	23722772		
*********					30T-A1J-A9	12143
			307777777	7233777777	7 777 3722.37	21222
		TTATOTOATT	SAWATTATAS	CASTTTATAG	3577772353	11153
AUTALAKTEA		727777777	7327717777	3072307772	70 35AA 663A	====:
TITITIALSA		TATABABBAB		7143434343	447777777	22367
7377777733	1070230701	<37777777777	$\neg \exists \lambda \exists \lambda \exists \lambda \exists \exists \exists \exists \lambda \lambda$	777734777	26.7.7.7.7.7.7	11,,1
DOTEMBETSA		1777437131	TEEENTENEN	TA INTITUTE	200300000	
00004474747		727171222	** =========			
TT024 2T00T			222277777	7207727777	TN0000000	11161
177777777		187777777	1277122777	72334,273,07	300ATT3030	11:11:
	1111111111	::::::::::::::::::::::::::::::::::::::		100000000000000000000000000000000000000	7777372777	22783
27277773284		77/770177	3403400000	A DT COUNTED TO	1777772222	11741
REFERENCE	18484444	7777273777	ACARDITICAL	SECONATION		12223
4277777777	- 3.3 (1.7 (1.7 (1.7 (1.7 (1.7 (1.7 (1.7 (1.7 (1.7 (1.7	1712771471	RETTETERED.			
V:53773323	4277777777	10.44.4.4.4.4.4.4.	3.273.277773	202200000		
1971/2000 TOT	72	7070404.11			1777774443	12711
1371773323	7777344744		9407477477	STTORTOLAT	7.5.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7	22333
3000000000		7773477-T-	773777777	TTTTTT	10-11777	21241
	ACCATTCTTA	TAPTINAUTY	TERUTTERA	ADADATEAST	322225	12127
TETTTT NAME	<u></u>	PASTTATTO	3777777377	JA ITTIAARTT	TTTTTTNAA.	12143
	73ATTTTTT	1200 TTN-13	AJAMATOOD	3737373473	44120000	
77111111111	JAA STOATES	284 2021 27K	744 TUT1 TUT	TATATAATTT		1.1::
TAA424.TTC	3A 137A 7777	-7444E5045	TAATTTTTTT	TETTTTAKA	77 1777 273	11111
3070377770	1773.48.27.13	773 237 277	7.5.7.5.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7.7	SCTTCATCAL	-~~	11,11
007340707	วรรมระนัน	323233333				
77777777	TIAIREADA		+ 23/20/20/20/20/2	\$4545455000	\$77777777	11.41
300032010		923 2377 23.2	ASSISTED	373.2 777.	::-::::::::::::::::::::::::::::::::::::	11511
	773237427	4774331477	Vatintiat	0010000000	10770000	11551
ATTRO NA DRO	700247424	3234477174	IT CONTINEN	7777777777	<i>₩.</i> ::::::::::::::::::::::::::::::::::::	1.4+1
1011111111	ASTATOCASA	3777344771	377777777	TSASTTTSSS	\$277 0 27 3 73	11701
TITTA SAGE SA	TTITTTAT	SATTTSTTT	2727337777	35 37, 32, 32 7 1	13401177501	21761
ATTOCTTOCT	ARCTACOTTO	AGAAGTTTAG	AARTTERTAR	TTTN55855	73.77.77.23.27	1:32:
TEATTRACTE	CACACCTTEX	TTASSEALLS	~~~~~			
	TATATTT NA	AUTTTTTTTA	~======================================	SATTTTSAGA	TTTTTTTTT	11331
AATTERETER	AACTT TOACA			AAT35AEETT	78737 777 7	11341
SASTAGENT		3077373773	TTATAMETA	TITGATINADA	77777777777	2,111
		SETNEMBRET	7778787777	TATITTITAT	127777771	1.15
TGAGTAGTTT	7777777	74 03444344 5	TOTOMORTET	TODOCTATES	13.773551 . 3	1.11.
ACCAL COTAL	47772444.74	7340000000	AGESTETS SAA	TEATERAST	DA DOTATAVA	2,22
AGAATAATIT	TAATTTAATA	TOTAL CALITY		3070777070	ACCCATTATE	1,1,1
TTALATOTTA	ACAACTTT	ADDTTATATE	TONOTTANT	2773224222		
STTASTATTT	ATTTTTTT	7474277744			TOTALGREET	2,111
STTTLASACT	ATACAGCTAS	700000000	SATNOSKAGS	TTAKSAST	TIACAACITT	2 (13)
30377104283]== ==== ===	7273737777	70730777	14427
	SUTATURATE		TTAGATATAT	NENGETHER		2
77777777		777775332473		* \$ * * <u>* 2 * * *</u> * \$ \$	1277772721	1.1.
	TTO AN ER EST	7,7,7,7		<u> 1, 2 - 1 </u>	:::::::::::::::::::::::::::::::::::::::	2
	T:::::::::::::::::::::::::::::::::::::	-: <u>:</u> :-				

FIGURE 5G

352447724	i watestasse	TASTSACTA	AACAATSATS	1511165111	10200	25260
130754737	I IAJAAAS TII					15110
	A ACCUMATES		- A. Addrew			
		AGAGE.			. Jannes Ja	25380
700000	: JAAJCTSCRO	~	TEXECUTAGE	AGAGGTTCST	7217323577	:244C
الممامات المحادد	AGCENTITE	ATTACATION	AGTGC XXXGT	IAAACAGCAA	STECTSSTAT	15500
AGAACCTCT.	S SCAAGTTATO	CAGAAGATET	NOCTAAGATO	ATTENTENAC	172227223	25560
TAACAGACT	TEAATETAGA	CONNECTE		*****		35420
	AGAGAAGTCA	170000000				
	7 7070777			-MAGGACAAG	TTSACTTTTT	25 6 8 C
	TSATSCAGET	3373AC	AGTTOAAGCO	AGTGCTCAAT	TAGEATTETS	15740
AAAATOTTAG	: GGCCCTTAAG	AATTATSSTA	TATOTACTOT	GCCCCCCA	CATACATOTA	25400
メニシャニシャルコス	TITEATEATA	3575777823	363735777	72477		25863
STICKARCE	T SETTAGACIA	3000 T		,		25320
AGTONOGRAC	AGCCCTAATS	71.51.51.51		~	340.40.00	
		STEE TOTAL	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		A-303	15380
3	CATTOTOTAG		MGAAGTAAA	TTAACTTTT	AASTATTATT	16040
4	TACACTITET	*********	CTTTTTTAGA	TAGTSATTAT	Charaktras	16100
		***********	3000073	30737	11.7771711	25150
JAA	30	AGTAGGTTT				
GTESATTET	ATTAAAATTA		*********			252.0
G1.77157777	**********	7070	44.mm-1		30.00	16130
	SAAGTTAATT	.~~	SECTIAGIST	ACACAAGTTA	GERGEETSET	16140
	TAAATATTA.	TTTAGATAT	ATTTAXATTT	TOUTTANANT	AATACITATA	25407
CTTSATATA	. AAASTTAA	30000000000	JUL . TATERE	AAGCATACEA	GCCCACACTC	25450
TTTTTTNACT	: cactttactt	773772X730	1155555			15320
7772277335	********	7377777744				
TACCAACTTC	13	- 10 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		nenu .nc		16330
CTTTTTTT				SEATTT TEET	77277753377	11141
		7777777777	TAATAATTT	7773737373	TTTTTATAT	26733
WATE TO ETAL		4747747784	44,773,737,73	3737737373	23 23 273 273	26763
30114211T	177177173	200000000000000000000000000000000000000			TROTOROTOT	16321
	727-27	7777227377	2277773.273			
NAT 17 17 17 1	737777777	17117777004				16111
32721217			:::::::::::::::::::::::::::::::::::::::	12777777	1777773	163-1
		TATEMAN TOT	TEATTTE	A244777777		27727
######################################	17777771111	100004445	2737237277	ATAGEARCEA	100 73 23 777	27151
- 777 7773373	337 7 X43 X24.	1077127744		ATTITACTAN		27122
STTARGETT	7377777327	TTTTATIALA		TTTCharact	NOTTOGTT 1A	
BOWN UNLAST						27137
WATTTTMALT	TTACCATTAT		AACACTAATT	TTOTOATOA	TT TALAKT TO :	27243
TTTTTTT		MITATION	TTTTATTTV	RAKTTTTAAR	XT TTX 30 0T 1	27222
		TRESTTABLE	STATEMENT SAME	PARTAMETET	77,973,07022	37343
TTIGAARGRI		AGEDEATIKA.	ATAGAGGTT	ACADDADTA	WASHING ST.	27423
777377AT	377777777	AAATATTTT	1737237227	ACCACTERICS.		27432
ACADTTICTI	303000000	\TTTTTTT\:		22 CT TAC STA		
30.533.5773.5	TTACTTTATE		7177177	2.7		17340
7777223327		1. 10 3A . 1	NE 2877 775	7273777773		17533
	The same of the sa	777777774	107341457	TERETTERE	777232777	17551
12111111111	AACCAALUT	17777377	₩ titt==U.i	AATAAAGGAG	TARATITITE	:- : :
W121171	TAAAAATTIT	77777777	111111111		kanasasa.	27732
7772772222	073200A244	\$0\$70000xx+7			7,7777777	17341
ADAAADAACA	TACTOCTICA	TATOCOCKÁL				
337 7 737773	ETTETALES.			TENTETTE .	FACCUCATOR	27327
TABETTEEAS	TETTALATET	300130000	5AAAAT NOAT	IT WATTEA:	SATATEACES	27960
7772713422		BESASSTERS	LAGATTITE	COTTO COCK		13011
	TTTAGTAGTS	7977777574	******	CONSTRUCT	TTTTNUCAAT	22790
3473711. \ 47		TITE ARTIST	TATTTACTES	COCTOCATE	TATTERAKTE	23243
CCCAARCTCC	727777733A	777777377	TTSATTATTT		TTTTTAGTTA	13101
PARRITTETTA	\$000TT%_A			TOTTOTINATA	******	
7007277727	1770770770					13160
7971771111	ACCOTOCAS		· · · · · · · · · · · · · · · · · · · 		TTT ST CT IN S	13111
		ateutitet.	7ATEASTSST	20273273	TTIACCCCCT	2:233
SCA OT DARGO	TATTOTOTIA	TOT INDCOME.	CCCACTACTT	BOSKITACAS .	AACATTOTAC	25-40
ENTERTENSE	TAATTTTTT	\$ 77777 777	~			13511
		M	·			
						11140
nakaa sebah				~		19611
	777777777	**********		777 777 \ - 77	NUNCTABLE	13431
	and the second second second					11111
			77 177 279 3 5			11221
4,					- '-	

FIGURE 5H

WITE TIT	TTINCTAAAT	TODATEDIAT	ACATOTTACT	TEAGTECAGA	X 	29460
SACRETRICAG	ASTSSTABAT	CT CACACTAA		****	72 77777	19510
3535557575	SETERCESETT	STAGATOTER	JAACTTT 355	ACCECTAGGE	COCCECATES	23540
COACCTTAGG	ROATCOAGGE	CATOTTOGET	AACACSSTSA	AACCCCCCTT	TTACTALLA	29540
TACTACATA	CODDCCCOOKT	COCCOCCEC	7300757.407	CCCUCTTACT	######################################	29700
AGGCRGGAGA	ATGGCGTGAA	III II	STACTITUES	SKEEDDAGEE	ATTTTTTTTA	23760
7523272235	COTTOGSTONE	AGAGERRIAC	toostataw	200000000000000000000000000000000000000	******	23820
		_				
TAAATAAATA	TTTAAGACE	ATACTICAAT	SJASSTOTTT			19880
	TTSSTSATAG	AGTTTTCACT	CTGT:CX:CGT:X	COCTAGAGES	1257305355	29940
ATHETTHOSE	TEXCTECAÃO	***************************************	TOOUTTERAS	223777777	TOTTENSOETT	30000
TESSALTAGE	TGGGACTACA	307300000	SEEMCTESSS	3072A-1117	TGTATTT 3.5	10060
TAGAGATTAG	STITCACTOT					
		377777777466	2723737732	ACTICTICACI	TEAGGERATE	30120
CYCCCCCCCC	200000000	ATTOTTOGGA	TTACAGGEST	GAGCCACAGT	SCETTSGCCCA	30130
SASSASATAT	TTAKTOAAAA	ATTACTACTA	TTAGATAGGC	AGATTTTAG	aaggaggga.	30240
TESPYTESSE	TUTTGGATAT	TOGACACAAT	AAGAAATATT	SASCTAAAAS	77772244	10200
TTTTTAGAGAGA	TACTITIACA	SSTAAACACT	TTSTAGAAGA	AASTAATSAA	TOAGACTTTC	30350
************	TTTTTAGGTT					
		TTTNOTTOTT		SCEETERIATE		33423
RECACARTAR	AAATAATAAT	AAAATTACTA	ATAMAGTOAA	TATATGAGAT	STERACTECT	30430
TEETTTATEA	CAATGTCCTG	TTTACTAL	:::::::::::::::::::::::::::::::::::::::	*************	ATCCCCCC.	305.0
GACAXATITT	TAXATEGTEG	AAAGCAAAGA	ANGANATTAT	ANANCATEAT	-2011-2101	30600
ALACUMUMT	TTTTTTTTT	GGAAAAACT.	TACATTTATT	SASASAATEA	TTACCAAGET	30540
GMACHT DAGC	TATATTGGTG	DASTEATACT	3 1112 \3155	TTTTTTTSACC		36723
	STATETALAGE	4540455045	73072777244	AACTTAAGA.	CONTRACTOR	13733
101111114	3324443373	758757755		320.0720.720	SACATETET	3 2 3 - 1
10344.0344.7	ACTOTTORGO					10911
		TAWATIOTE	70077770033	DACCTCCTAL	ADAATAADIA	
TTTTTTTAA	12X77711VA	ASTABI CTIC	45AA333A33	777777337	1124111 111	10341
77723373372	TA DA CONTRACA	RARITARITA	~~~	TRESETTEAT		11111
AAAA DATITI	ROTTATITES	77775-4-347	1912111444	437427777		1111
*********	37777337777	140000000	77773	12-2-27-7		1111
TAMATTATAA		944 TOTOCT	ITTEEAS FITT	AAAJITIJAA	377377777	1111
CCTRICKSTT	TOTTRICALI	7200220077	7777777777	TA12ATTTT	7773477777	1.15.1
**********	327.5470777	777777147%	17341771147	TTINTATAT	1111111111111111	1.111
***********	*********	35			1704023777	1.111
			TATESCETOR			
GENERALET.	33 TTT AC 2333	7777 77 77 V.	3272232273	SCRETCTA	TAXTGENTNE	11,.1
totoakaka	7733233327	#ECHCOTREA	DDCD A DA DTA	CTACACTACC	ACTERCECTER.	11111
703003.0777	3077077007	73.03.277.077	13077777733	3527753337	27.1 57.77. **	11341
7733773337	3732377763	727.2773753	WATERAARTE		2000303727	11611
300224 - 0335	1017713357	4 DAMAKTNIA				
			3070710007	TAGTATAA	10000000000000000000000000000000000000	1 2 3 3 3
401111900 17/10	STITUALIS	47377XX335	3773777777	AUTTTINAUA	13071071114	117-2
40 1777 1 2 2 1	RECERENCE	784777742 7	TTASALAAAT		CATEAATA	11100
	TOSTTTTTTA	ATTTNETE T	777777777	CATATACACT	47.77.77.73.73	11361
SCTTTDAATT	************	7307777373	T	7575244477	***********	11311
ASTERSTOR	TOORAGEORA					
		ATTATAATTT	777747737T	TEXELVICIN	7372773277	1.960
100700001	STTTACTALL	7777777	77702000	DANKSTRETT'S	777777777	32343
TEARTRETS	3737737773	ATRETERATO	SOTTATION	2273427277	TTTTNSAACA	12111
SSAAAATSAA	STACICIALA	ACCTAMATES	********	1007175224	COTTTSTEAM	11111
00000000000	AGAGAGATE	ACTOCTOATE	7777734774			31111
######################################	************			J	TEATTAIT.	
		********	ALCONOTETA	3.7.27.7.7.7.7.2	402 443 1777	32232
9 77 277 027 0	ASTITENTEN	3000000		ATTTTTTAAGT	*****	32143
STTSTERCAL	TACACATTICA	AVATTA EVA	TATEACAEAT	ATTWACACA	TTAKSATSSS	32400
552255552	AAATATIITA	AWATATTT	ATATAMATAS	ATTTTTTTAG	AATTTTTAJA	32,433
ARCETETTA	CAAAAT WEED	ATATAATTIA				
			TAMATOTISES	NTT NAAGAST	TTAAGGATAT	32223
22444	TŞIZMAZTA	AT STEENANTA	ATNOTESTING	3243373633	1.4.044.777.1	12537
ATTITACTES	TETAMARTET	ARTORARTOS	737777377	2000000000	SCCADDETT:	02640
SSICKIAC	TESSETTERAL	CTTTTTT A DOC'T	JACOTTOCAC	TANGETSAGA	1007000	12733
GCACTICACC	0700000333	GACCONSACT	7237272.	*********	1207373713	32767
ACTTOTATE	1373347375					
		TAGAAATAT	37773	WARANTTON	1505735033	11111
CASCSTASTT	ACAAAATITT	78400kT: T T	1373444744	73,277,777	3447343437	11331
T04 T0444 20	1007027007	2014-7-777-17-	10000000	1727373737	7772273737	111.1
111 / No. 7 No	0.0000000000000000000000000000000000000	4444311211	4272577547	TAMECOALS	13 Taxa Taxas	
	- ::: - : : : : : : : : : : : : : : : :					
	·	-				

FIGURE 51

						13550
ACACTIATAT	TTATACACAC	ATACACATAA	**CC***CCTTC	AATAGATSGS	.,0.,0.,0.,	33723
TTATTCCCCL	AAAIIIIAACT	ACTITIONAL	ANGACACATT	AGACTITA	JA JC-04-1	11780
ATTABBACTS	AAATSCTSSS	TTAGACCATS	3737730527	ACTGGGGTGA	CONTRACTOR OF THE PARTY	33.60
TAGCENALIN	130111111111111111111111111111111111111	SSSATAMATE	X	GGTGGGATTT		33300
	TTATTATGAA	SCTSTAAAA	AGNAAACANG	شند و المالية		13960
1011113113	34414744	ATSCTEAGAA	THE SAME TO	CONCECTIVE	30777	
TTTAMETAT		CACACTETAC	TTTAGCTCTC	AGATTTTT	ACATTIANA	34020
TOTANTOTOS	IAAAUTATTT	3002450422	TTTTATTTCC	TTGGGTGAGA	TAXTTOXXXC	34080
ATTAGGGGGTT	ATATATATAG	CATGTAAAAA	STANANCISA	AACATTTATS		34140
ASCASTAVAT	TAGTACTENA	CTAATAATT	TOTTAMOTO	COTTANTANCA	TATTATAA	34200
ACCAGAGAGA	AATTTTTT	AAAGAAGAGC	TERTEGREAC	ATTICTTEAT	ATATOTATAC	34250
ATAATATAGT	AGAACACATS	ATAAATAACT	TATAAAAATS	ATACCAATAT	CATTERTON	34350
5 2 32532555	TETTETTAA	ATTATTAATT	TEXTETETA	CAGGTTTTAT	TATTACTOTA	34390
3727377777	TTEXTETACE	77777777777	ACTTANANA	ATAGTTTT	ATCTCTTAC	34440
		AGATTICATT				34530
		ATT TT				14560
		TOATTTAAAA				34520
		SSTTATAGTA				34630
		**********				34740
10		TTTTAGTCC			35.573.55666	34300
		772772223				34850
		20.00 				34377
3775277373					ATNEATATAT	24981
						38343
	TATTEATAT	3	TITIOTA OA.		STAGAZAGAS	35123
77 77 77 77			. GREAAGAGT:		AAAAAAAA	13161
		13.2223237	: ASATASTST	TATTULAACA	TACAACAAA	
	· 2000000	10.77777.00.0	2	: tagtttatet	: AAACTTITIT	15001
		NAME OF THE	. ITTIIIIANTI	\ \ \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	ACCTTACMAT	11111
AARTTT IKS		· 77777344433	SAATSTTST	: ::::::::::		352+3
	: which	. ACTTTAGTT	T DOCEATEAN	E AT TIT TIAG	A DATTITATU	13,00
	T AMACACATT	: ATABETTKE:	D DATACTICA	TAGCOATAT	TTAAAATTIC	18461
ACTAACAST.	TAAAAA STAC	CAAATATTIK	i kotottka:	K AACAATOTI.	A REATTERNATE A	15523
4344444.000	A AGETTERACE	CACAGGAC	N ANDSTRAKS	: tatataa.t.	\	18880
TATACTIAC	\	A TOTTOTALIA	A HARTADADA	: TOPATOTO	: Decominat	35543
23A 22A-27	TOTAL AND THE	TITTAAAAS	7 70077777		7 073,073,0707	3 5 7 5 3
TTT 1/17 1 TT	TTTTAAAAC	4 4000AATTS	TTTNACAA	T TACCATACS	* *************	19743
	x	: :::::::::::::	: ::::::::::::::::::::::::::::::::::::	o ACCEACGEA	G ATCATTCAE	15321
222322237	t toagaddic	T TOCADAADA	DORDADDUK T	t tototttac	T ************************************	15337
WATTABET	t 300000.000	1 000370077		A TACTTICCA	7/24242222 L	15940
202427723	a tealcoele	diacocacaca	T TEERGTERS	t TOAGATTEE	S ACACTOCATT	15000
25.24.23730					A ACADEATATO	35252
TAATTITT		T AASATALAST		S TTSAGSTT		35121
	T 443777773	T 555275553	1 111177177	3033777	A STITEMETTE	36130
1				- 31-1-3-5	: ATTTTTTT	16140
111 114772					+ 5110A30111	35000
					C TOAKTAKET C	15050
					E CAASAAACEA	35420
					TTTMETTES	35-60
	3 TAAACAA	A 000000	a management	- 27777777	AT ATACTTAATT	36340
				· · · · · · · · · · · · · · · · · · ·	T ATTESTTEEN	36500
					TT CATGISTIAS	35553
		A ANTOTONA			73 TETTTT35TA	35720
					TERREPARET TO	
					NA TEAMTERSON	36340
	· · · · · · · · · · · · · · · · · · ·				CE CTEATATEAT	36900
					A WOUTHOUT	36760
				~ ~~~~~~		37773
					ra catteriesa	
A ACAUTT	^~~!!!!!			on indeparts	TE WATAGETTA	17141
333773357			TT NAAASAAT	UT TOTAL TA	AT AMATATITIA	17111
12.7571777			-5 33737373	~ :A:0:A2T	se tottokioto	
			ii i ntit ita		77 1 77 177 7	

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DE LE CONTRACTO DE LA CONTRACTO DE LA CONTRACTOR DEL CONTRACTOR DE LA CONTRACTOR DELA CONTRACTOR DE LA CONTR
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FIGURE 5J

ATT 112211		TESENTEENS	TTATCCCUAG	22 273244 52	7555775555	CSETE
TTT IAT TO U	racaracrea	TETTACTOCA	SAGGTTCAGA	AGATTATTEE	TOATOTTATE	17920
10222	COSTS ACTS	ASSTSAGAGG	CATGGCCTAG	TTTTCACTE	TTAKESACTE	37980
SATSAASTAA	ACAMOENTE	CACTATATA	772307773	SCHOOLSTEN	70777777	38040
TATTATOAAA	ACCETANCE	TGTGATT		***********	3	18100
1237737230	723.5555556	STATACTSAG			37777773745	38160
203020		TTAGGETSGA				38220
			7.3440.335	J.JA		
	22.500	STSATTETE	.uc.:Lhuc.			3828C
70003.3.3.		AGCTACTTT	TGTATTTTT	אבאבאבאבא	3337777777	38340
	30.50077777	**CTCCTC*C	TT TT SATISAT	ccccccccc	2,300000	18400
**********	ATTACAGGTG	TEASCEATES	# CTTSSCE	ATACACTIA	****	38460
**********	AGCTTAAGGT	TACAACTTEE	CONCONTOCK	AAACSTSCAC	*******	38520
***************************************	C171017710	ACTTOCALLA	ACCATATITE	TOTOCACATT	23.77.7523.67	1653C
ACCTTCCTCA	CTCCTAGTTC	TTESSTAAAT	COTTOTICALOT	CCTTGTCATT	35 111 535 11	38640
GAGTAGCETT	TOTAXTONAC	ACRETCATTO	STATCASTTA	CTSTCACATS	32252525	38700
ACCAAGTTCT	STOSSCEET	ACSTAGAAGG	**********	*******	AGAACTTEAG	39760
CTCCCCCAGA	GCAAGCCCCT	TTGCTTGCCC	7373666673			38820
	AGAASTAAAT	AGGAGATACT			-1	38886
TACHASTTE	SSSTETTATA	ACTERATARA				38940
GAGCAGTIGG	7272772272	SCOTONICTO				19000
		TOAACAATTT			ATTTTTTAAAGA	19060
			UTTAAAT 1014		Antimotical	39111
	JUNTATITE	.AUALIAG	TOTOLOTTOL	***************************************	AAAAA IAAA	33730
	ACTTORATE				ASSEARESEA	19140
AGTTOCACTA		WASTT STAGE	TATESSESS:	RETERETARE	CENTTTCACE	19111
	NATAR DOTA		STOTEMETER		ATACAAAAIT	19141
AAATA ITTI CA	7277277327	TA INA GENER	400TAAA0TT	307777777	TATATA	3 2 4 2 3
7724242322	:::::::::::::::::::::::::::::::::::::::	10000000	272720722	322327777	DAGAGOTTAGA	13431
TODASCIATE	0277020000		CACCACCAC		1010: 2001	19541
37.77.77.33		4477400000			1272731377	19411
ASTTTTTALE					ATAATAACTT	13441
2004014003					171711111111111111111111111111111111111	39713
		ATTALACIOT	77-71-71-7		W000000	29732
00000000000	3777734	NEASTSCTTS				33347
						19911
2.	7,550,500,500,500,500				A CONTRACTOR	
	AAATAACST		10	haddilada.	ATATIAN .	19963
					CONTRACT	43023
3347344777		- MAN TTATAT			: dodkadakam	40383
2000000000		, Presidentes	140 111 000	. :::::::::::::::::::::::::::::::::::::	: tothextexe	40140
TTIAITTIAI	3778378277	: IAAJACIAI		. TOSTONALC	: :::::::::::::::::::::::::::::::::::::	40200
TIMOTALA		: AUGMETEETE	SEATSCOOT	T ETHATECEN	ADDADTE TE	40260
DACT DACC TA	. 35,44,755	: TTSAACTTS	: JAGGCGGAG:	ttstksttk:	TADTAGATCAT	42323
500% 0T 10% 2	773/2022	: ittacacast	SACACTOTO	TTTMAMA		40130
AAGADETTST	NECTTER EACH	STTTTTACTTT	TTTCACCAG	TATACAATT	T ACAATOACTO	43443
AAGA TTODAS	. WATETTA	ATITTAATTA	230347343	T STAAAASSA	I AAAAAATTAII	40500
TAATOTOATO	TOADONACK	درنده مدهده د	TEAMAGEEN	. TAAAAATTI		40350
#A####################################	TATITIALS	. ACCAATTOTO	TTTTTTTT	- 537777753	T TTT CTTATTA	40520
TAXETTTEET	TOTAGATOTO	TATOTAAJEA			T AATETTAGTA	40480
######################################	TGATASTTAS	3227.32			N TITTOSTOAAS	40740
============= =======================	. 00%*****	AGUTTAA:""	101.0401.0		T TOTRALACAT	40900
COMMODITACE	173345451				3 3703-2077	40960
	1	TEMPERATE	· JAGACGAAA	. ~~~	2 7777730337	40322
				/ ~^.	5 000000000	
		• • • • • • • • • • • • • • • • • • •		/ W. JAJA. S	1 TT11TTTAGA	42953
		· • • • • • • • • • • • • • • • • • • •		i Juna		
	· · · · · · · · · · · · · · · · · · ·			. ISAISASAI	A TTOAGTAATA	41100
			TTUGUCACA	i mima	CODERATORS S	41153
70.74	. JAG-175A2	- 1565ZA35T	TEDDADITE	A DETETTERA	a Rodrodotor	41111
22.5.23.72.27	344400000	i ittitaetaa	A AATACIRAA	A TINGGTOGG	i thististka	41230
ACREETOTAL	N TOTOMOTTA.	TTTTTTAAGET	ACCACCA	i wittetti	a 4000000000000000000000000000000000000	42242
440070040	,	C CENAGATET	OT CATTOTA	1 711417777	a kawkawanat	4,433
		0 1000000000	+ +: -:::::::::::::::::::::::::::::::::::			• * * * * * *
T	: :::					
					_	

FIGURE 5K

						42060
CACCULTURA	ATTOCAGCAC	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	TINGUCAGGC	AGATCACTTG	Actor and a second	42120
	3027750000	CATGATGAAA	***************************************	ATTAMASTA	200000000000000000000000000000000000000	4212C
7770565.00	.3777553736	TIGITAATUUT	AGCTATTERG	SAGGETSAGG	Chinamana.	12240
303	ADDAGO TECA	301.104.11	AGTEAAGATT	STEESTACTES ANAMAGAGA	40	12300
JUGAUACAUA				TEEGACTTEE		12360
			JOTTSCACCE	STOCACTOCT		12120
				ACTUTACET		12480
	1000000	~~~~~~~~		AAAATTTATO	~~	12540
						12600
				TATIBATTAA		12560
				STACAGETAT SATTTTSTTA		12720
						12780
				CONCACATOR		12340
				SATAACAATS		12900
				ThinninThi		42960
						43023
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	70707.770	***********		TATEATTTTT GCAGCAAGGT	***********	43080
				TOTOATOTTA		43240
				CTAATGGATA		43200
				ATGACTGTAA		43253
				TECERALITAE		42430
177177777		10110177	777.33.00	277777444	TACTUTURA	43230
				TANCANTOTA		42442
110000000000	721171177			ADSTRATAGE :		43333
				10070007		+1560
7171771217	1100000				7573423773	41620
						11483
TATTIA DALI					TAATTTITT	43743
	TARETARA			134447714	CTEGRAATER	43300
TTX23,2TTT		222232777		343565777	ACCETTAGAG	13350
		1 400070777	. ASATTAATA	170242335	***************************************	43922
307777777	- A437777327	T DODANTE NA	773444344	344474755		40980
TTTATATAT	ATATTITAT	ATAMATETT		Tilaanii	1.00 0000000	44040
ATM/T03277	113131111	377737733	77	. TREEEETTAS	TTTTNAAGTA	44111
					AUTTAUTANA	44161
Quantities.					TATATANA	44221
	1007777	K TITAGAATA	. ABBABBTTA	- 344267777	4734373733	44231
127277777				<del></del>		44242
ga ca calatica			. :::::::::::::::::::::::::::::::::::::			44400
10000000000	ASSISTESA	: CACACTTCC:	: TAATTTTA	. 373777777	T AGAGATGAGT	4-4-50
TOT CASTACT	* TTTCTTMCT	i tastittia	3000000000	TAAGCTATT	t toockettik	4-520
300700012	. GTESTGGA:	: TACACCTET:	RODERSTER	100%3000	* ************************************	44550
TTT 1AT 1 1 1 1	S DAGTEREAS	I CATTAMACT	: 7 <b>11.</b> 177771	S ATOTOACAT		44547
877777877	. <del> </del>	NATACTIC	t tattatat.	: :TSSASAAA	A CATTOTTICA	44700
TTATAAATTI					T CASATATOTT	44763
ATTTTIATA	7777777	C TOTAGECKE	I TOUGHT W	t ttasas <del>ttt</del>	T AMEMBERS T	44323
					T ATTITATIAT	44937
SATACAATA1	T TTACTTAGA	A ATAGGGTAA	T TATSAATTS	A CAAAAACATA	S CTATTAATTT	44943
		T AGATTTTT	I 733 <b>~</b>	s <del>TTS</del> NIKTTT	· whichdettt	45000
STACTITION	- <del> </del>	- <del></del>			T 07777777777	45353
77999277			T TAAGGEATT			45122
					TERRESIDE T	43130
7777.	A TOTACTACA	A WCTAUGGT	7 847372372	T CTTTTIALA	E ACTEMACE	45242
TOTACIONI	. 377370A <del>77</del>	A ATTITIONS	T AGATAI <del>III</del>	C ACCAUTTAT	אַסָּפָנדאַנאָד ד	45300
91.A3A33A	u sulaagatt 1 su <del>laan</del> sal	- 401/07/04	J	A	a tatata <b>tak</b> a	45350
ACCIACIAT	- <b>~</b> ::::::::::::::::::::::::::::::::::::	. AUAAATATA	A AUGUTACTI	A TAGAMATT	A TTAGAAAAAT	45420
373773377		A TOTAL 22-27	T ANDTOTAN	.5 KTTT%-0TT	T WATERTINA	45437
					TERREAL L	
	u neusikkast 	5.4.4.4.4.5 	n Baatkaaat			45600
		- 14 147747	- 1770 P. 177	- :-:-:	·	
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					er emittet⇔tk	40
		i en en en en en en General en en en en en	2220.5.		- · · · :- · · · · · · · · · · · · · · ·	10
			r rususeusi		. Sa	

#### FIGURE 5L

AASTMATTS	TOLTECT TAC	ATACAACAGA		: <del></del> ::::::::::	1171111713	46250
TANASTTOO	2011	DOATACTACT		JACCHAJAGA		46320
TT30TTT00		TEATENTERE	STTSCTSATT	TACTATOTA	71/24/77/77	+638C
	T.Man.T.T.			CACTTACTTA		16440
SCTSTSTAAC		TOTTTTTTT	TTAGTTAACT		30171777	46500
TOCACTATET		TOCACTACCA		TOGANIANA	ZANATATAA	16360
ACTTONAMO	TOATAATTI			TEXTETTERA	AATANCIISA	+6520
***************************************	ACITALITIE		TTTCAGGTTG		TAXATTAGGT	466ac
SACATSAST	SAGTAGETTS	TAACTICTT	CAAATATTTT	ATATOTTTTG		46740
SANTSTEATS			GGGTTTACCS		21.77522623	46800
		STSCTSAAAC			AGGAGGGTGC	
TACATAATTT	720220777			AATTAGTTET	5 <del>7.7</del> 5%5 <del>7.7</del> 5	16860
AAAAATSTSE STTAATSTSE	***************************************			STTCCCAGAA		45920
		ATTUATUTET	STICTIATES		CATTERARGA	46383
ATCTTTTTA		ATTTACAGGT		TOTATTTAM		47040
			AUTUATEAUA		TTALGAGIAA	47100
AACTAATTAT			AGCACAATTT	CCTTTAGAAC		17150
			AAAAGACAST			+-===
		STTT SOATET	733263		SATACTITAS	47230
	YELLETYLLE		SSCTATAGGC			47340
<del></del> 555cxxc		COTTTOTACA	GAATATTTA	STATTTTAG	## ###################################	47400
********		TATTTTCA	AATSSAST!.		TACAGATATG	47450
AGTANASTTA	3000000	AATSTTASTT	177722221.00	TTCACACCTA		4 1111
	AGATIITTAA	ACATOCTICE	DACACOTOR D	77 033 2777	ATOTOATOTO	*****
WCWANICA	SATSTITTES	COGTTOTTAK	SAGATITITT	TAASTTETAA	SAASCAAC	*****
:AACAACTAC	CATCATAC	TORBOTATER	ATTATATATA	1447777147	CASTOTICA C	::
	77721737777	TAGTACTAGA	ATIOTOTATE	TTTTTT:AACT	TTTTTTAATT	+7751
TT \$3.77.773.7	73,2727,07,07	ATETOTTALA		777777777		+7111
DANAGET CAT	TAXXXXXXX	A SACTAGGE 3	SSASSTTTALS	7,77,777,777	7.0000000	47983
TOTACALITOT	CASSTTAAAS	777827773	. :::::::::::::::::::::::::::::::::::::	100000000000000000000000000000000000000		-73-1
TTT 103A35T	3232773273	34 TTT344 3 CA		1310131113	. KTTAAAAGTTA	48000
APA SARATTS	7377373	scottorews.		STEATTOTA		12161
5575757733	TATEATATTS	AATATITIAS				48121
ACCATTICET	#97 <b>35777</b> 73	TATEATEASA				48185
12213.02777	TATTAAAATT	<b>WATTTT</b> :				43141
AAATATIMAT	INDATATATE	17772A7247				43111
**********	STTSSSTATS	770000000				45161
JCAAL TEXTT	AA TTAAAAA					+3+11
:::::::::::::::::::::::::::::::::::::::	773777773					131::
7272002727	ICACCAATTA					43543
AT TTTTTA-		TUAGTTABB				43400
<b>₩</b> ₹₽₽₽₽₽₽₽₽₽						+622.
<b>₩</b> CA TTALAA C		TTCASTSCA				43727
<del></del> 3						43731
						48840
37 0444 0477						48777
**********						48960
T000T000A				AGSTATACT		49020
<del></del>						49033
407037003	AGENTATET					45143
TOTTCCA000		AATTTOTER				43200
A						49261
~~\TTTTTT						43121
					T SATAATTITI	49383
477735737	: 237 <b>2637</b> 32	TESTESA .			T TTXTTTTTT	49440
***************************************	7.33477471			1	T TOTTAMICA	
73.27	727771	1 74771			T STSCTATALL	49560
	37777	. 222337777	~		1 ATTETTTE	43410
	77777		·	- <del></del> -	7 77777 <b>*</b>	19633
2077773	***************************************					43 41
334077777	7374	1 11		in and states the state of the	T TATELTARI	49813
14111111				. 3.3-3.5.5.		177-7
					- *	

#### FIGURE 5M

~~~~~~~		TOTICKTT.VAT	<del></del>	3077727000	TUTUUSCOTAT	50460
		-7UA-A-				50520
		· • • • • • • • • • • • • • • • • • • •		*****		50520
~~~		000				
******	TACTITUTE				~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	50 <b>6</b> 40
2,507,507,50		***********	~	SATTANAGE	70.37.73	507 <b>0</b> 0
		CAGTACCTTC	TEETTEETATE	753,777		53750
		· · · · · · · · · · · · · · · · · · ·				53820
	, _ , _ , _ ,				**	508ac
						50940
AACTAMATAT	ATSSATTSAT		11-71			
ATTTTTA	TTOCTTACAT		`~:	~~		\$1000
5.0		COUTATOTAC	ALALALAN. J	AUCTON: DAG		27362
10107777	CTTAATSSTA	~~~~	AACAGAGTTG	SCACTATIA	AAAGATGTAA	31110
	************		TTTAGTGTTC	TACTSATGAA	SCALATAGAC	51140
	~		_,_,_,_,_		****	51240
	* **	A. A.				51300
	<del></del>			~~~~		51360
737077777	TATTTACAT			3	3000 TAGGA	51420
ASTA TA				AGAATTTAGT	SATSTIATST	31490
2-2-2	2017770707	J. JANJACJ.	TGANGETTAN	JTAACACSCA	TAATAAGGTT	51540
					TTTSAAGTGT	51500
			~ ` ~~~			51660
						31723
		7				
AAA JATTAAA	Wattoccowa	4,771	22 22 22 22	~~	**********	31733
NOTE: NO.	202022422	2117777			403.TTATTT	31341
	7007320773	51.75.00.00.00	***********	ATTACAAAACA	TODALARTOO	51311
1,7===1=1		-0	\$	TOTALOTORT	ASTATITAL	11341
	AST TOTAL CO	200000000000000000000000000000000000000		22727777	ATTTTTTA	32323
		* * * = = = - * = 1	<del></del>	PRESENTAT	ITITIAAASI	51010
		7777777777				321,1
TAARTRINAR	2000 13 13 15 1					
	<del></del>				ACTOT AAA	:::::
AATATETAJA	73277777337		ATRATTRAKAS		2272A22AA2	51151
A2323 *: *==			-nhihakidd	737777777	7777300773	31111
	7273.2273.2	Carrier and Carrier	22772723333	AAATOOOTOA	2002 2000 C	57232
			1035777.127	CATGATGGAA		32440
			3327725	337273734		50310
TATTAAAAAA	7732273277	~~~	:	1		51351
COMMINITA			Totalesser			12621
SETERTARE	7927234207	SSACTICACT	SGEGTGATTS	~~~~~	······································	
<del>- 11   1</del>   17   18   18   17   18   18   18   18	TERETEATES	TOSCHARSTS				32660
ACCOTTABA?	73.77			תשטבי באבי	2,422724022	52740
STOASOTOOT		701111111		DDDAGATTDG	<del>12111</del> 23233	50300
SAASTESATE		TOARASTOTT	313575555	ATSTITUTE	TT	52360
		ETTECATTAS	727372825	44.5444		51910
ATTATTAL	~~~~~~					80960
TOGRECASTS			77			13040
ATATACTT.			-1.7.			33133
TERREALTER	ACT DARK STOR	AACCAACTAC	100100000	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	~~~	
ACATITITAD	TTACTORATIO	AGGTGTTTTS	11	3:333333	~	33151
ASTAATTSSE	7024244	1-1-1-1-1		400.000.30	TOAGATTUCK	3322:
ATTEAGAAAT		ATSTASTSAT		ATATTTST	<del>77</del> 3,2777777	53233
STSTATTERS		PATATUALTA	777777733	ATGGGGGAGA	AAGGATGGGT	33340
ATTTSATTT	2000 2 - 1 - 2 - 2 - 2 - 2		TAX TT AAT 1		T17T17111	53400
			101			31451
TACCTOTOTO		Jun - 1	~~. ~~			51521
9555435777		d				53530
						53543
						50700
AAATTACACT	720727,323			.,4.57.27.27.3.	ACAJAATATT	33.760
						33320
						30330
						31941
						1,211
TALATIOTT	STTRAKTOOT	877427774	20022713-1	.,,,,=:::::		
			•			

The control of the co

#### FIGURE 5N

						54663
			.40.55555	TATTANATAT	3.30.0.3.	
0	-A. 300	JCATTTT-1.	30777775757	***********	AATACUUTUT	54720
344141111		CATOMACTAC	SCACAGACAC	STOTESTEEN	TSCETAGGTA	54780
	TEELIGOAGAA	304000000	SATTATTEA	STTSCTART	SAATTTGCTG	54840
=======================================	100011001	TTTTCACTCA	AAAGAATGAC	*********	CONTONTION	549QC
TTATTAGATT	TOURTSTITE	300000000000000000000000000000000000000	TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT	SAACTAAGTT	330 <del>011111</del> 21	54960
222	STESTATIO	TTTTTGCCNAT	GATAMATTS	SASATTTST.	SERARATETA	55020
TAATTTTTTA	AAAGTTGTGT	************	SAASSTERAS	ACCUTATION	AACATAAAA	55080
<del></del> -		CACTACTACT	101111	ACTESTED A		55140
			7077077	TTTTTTTT		3320C
<del></del>						
**********					CCTTCCT3CT	55260
			10111001100	CTCCCTCCCT		55320
			75757575	<del></del>		55380
7.7777777777777777777777777777777777777	7777722430	ACTOCTOCCO	CCTTAGTCCC	TOATAATAGT	SGGATTATAG	55440
GTGTGACCCA	<u> </u>	CONTRACTOR	AGCCTTTCT	AATSAGATSS	ATAGTAATTA	55500
ACAAATTTTA	STITITISATA	TTATATANAG	ATTITUES	TTTTTC3233	300000000	55560
CTERSTORAT	CASTATUTE	7303736573	2-1	TIMIMATE	1-11-110	55623
cessaseess	Tagettagete			COACCCCACC		33423
1071717717	31.51775171		7007010	AAACCCCCCC		55740
1777			222222	^~~		
*********		.300.755	TOCTIATIAT	CCCAGCTACT	5333 <b>X33</b> 573	55000
ALAUCAUAUA	4-10-11	TT TAGGAGG	35AGATT3CA	JTSAGETSAJ	AC : 333537.5	55360
TICATILLAG	::TTGC:3XCX	3435343457	2007070,000	*******	SALATERTSA	3 3 9 2 3
TT CCCTAAAA	32727277	<b>JASTACRASA</b>	TOGACCAACC	2277722727	37777233737	55380
<b>*******</b> *****************************	344440777	ATTIATATA	TTTCXCATTS	TACACTOCAL		160.1
4544-17177	A077077030	TTTTT 32714	117777	AACAATITII		34100
3AA (110000)			7771 777	ICTTITIESA		34141
<del></del>		11717	70.000.000.	TOAATOONIA		56111
AGASTRONOS		**********				
		*********	3.4020	1.0444.717.54		1411
			- <del>}-</del>		13,011111111	: d : . :
					WITTIW.	19401
GTTCT NOT CA				7533377777		54-40
TTTT143 33.2T		TITINGADIT	- RAGAGATTCA	COMMITTEE		54520
TATTRIAMAS	972722747	<b>AATTATITAI</b>	2773277237	3777777333	ATTIMATTTE	19954
	- <del> </del>	WCAGCASTS				5111
<b>TTTT</b>		TOGASTORAS		. ENGACATEAT		36*33
T3.T3.2.7.77.7.7				• •• • • • • • • • • • • • • • • • • • •	, katharmas	55753
A051713033	7723773		277774474			56323
7.27171.73					ATESTATAGE	
		101.100000	JA-AUALAUA	• • • • • • • • • • • • • • • • • • • •	727777777	56330
	700407774				3.77 <b>7777337</b> 3	56741
ACCOTTONIC			. IDAJAATAAT	• • • • • • • • • • • • • • • • • • • •	STATTIATT	37000
300+007070	300000000000000000000000000000000000000	300030	TAGTAACAS	:	COCCATORS :	57763
7070000440	77855555		TTTTTT			57123
TEAGRAPA DAT	JGGACATTKA	TTT T T T T T T T		: :c::::::::::::::::::::::::::::::::::	A RESAUGACET	57181
3777773337	700%377000	7723377277	ACACAACTAC	: ACCCATUTE		57140
GASSTERIA	23.23.2213.23	AGATOTANAS		CTCAAAGGA	3755AX7777	57300
AGAGATIOTT	3020002300	3133155	~~~~~~		S AGGETTETTS	57040
JATITTIKAT			·		TAADACAAT	
	777777		3735		31,100,100,100,100	97423
AGGARAFITI					A STANKTONA	57430
		- unuudaanta	ACCOMMOTATE	C CAGATOSCT		5 7 5 + 3
ACTORCECT	3.1.40.40.70		್ ದುರ್ಯವರಗಳು			51600
<del>111</del> 11111111	39AA737AA		ATGAGAGGGGA	t Todata		57550
ATAIAAATIT			, geototskt	: JG <del>TT</del> GCT <del>T</del> T	C CACAACCAAT	57727
CASATOSTTS	TATAGGGTST	100000000000	307723030	3735733243	: TISTIGAAGT	3 77 3 0
GGTTGAAGGG	TEGAAGGGCT	`	773772377	107537773		57343
<b>~~</b> 5000000	. TTGGTTCTT	1077777300	2 227077857		::-:-	27333
SCATESTATA	7777777				7777347723	5734
AGACATTAAG	- <b>3</b> 55 <del>51</del> 5522	. :::::::			7 7777342477	
3356	17171711	1551225		~	T 1544733333	
15.5.1			- 10000			13-3-
		. <del></del>	. 3/4400000.4.	2 4 <b>337</b> 43217	T TOTAL COLLECT	33141
				, <u></u> -/		352
7.3	*, */* . *			4	. ::::::::::::::::::::::::::::::::::::	
::::::::::::::::::::::::::::::::::::::	7.27771211.			- 2734723	. :::::::::::::::::::::::::::::::::::::	5635
107000000	. ::::::::::::::::::::::::::::::::::::	: Jakaaaaa	o swatatesk	: TNENSENS:		1172
A32331. FF :		1117777	:			3 1 1 2 .
				· · · · · · · · · · · · · · · · · · ·		

#### FIGURE 50

78577777	77.07.34.73.34	TTTTTTTTTT	TTATIGAAA	1.511	225232322	58860
			SGSSTASCTS			54925
			JAACATAATE			53980
			TAAACETTTSA			59040
			STEATSTEET			59100
			TTSASATAAT			
						59150
XTTX TTTTT		3.000.3.3	TENTTSAAA	ALIMANA	JC	59220
			ATTTGCCTTT	X17X7733X5	ATATT A-A	59280
TOATTITA	ACTITIONAL	CAACATACAAC	TATTTAAACA	3,7770,077	20000000000000000000000000000000000000	53340
GATATOTAAT	AGGTTACTTT	TAATCACTAC	TAXATTACTA	CAATTACTAT	ATTITIVE AND A	534GC
TATOSATTOS	TTAXAGEES	SACCTTT: AT	TATOTOTONS	AAAATTAATT	AAACTTTAGC	59460
CTCATAATCA	ICTTIXITE	ಹಾಸಿಯಾಸಿಕ	STITALALA	てのみこれんごされて	STATTATACT	53520
TATTEATOTE	TTCATTCAGT	AAACATTTTC	ATTTSTAGCA	TOCANGACAA	CATOCTAGAC	59580
ACACGAAAGA	TEGRATALA		<b>ತಮಿಸಿದಿಸಿದನಿ</b>	TOTONICO	AAGAGGGACA	59640
SATTIACTOT	GAAGATTCAA	75244444424	TOCACAMOA	ACTITICAC	*****	597CC
ACATTERNA	SAAAACATTT	**********	5305555	~~~	TARTECTAGE	59760
ACTITICICAL	3000200720	272237737	AGGTCAGAAG		72.77700730	59820
7275575222		1071111171	CATTACACE		376.300012	59830
	1.7-1.7-0.7	71.77	TAGGAGATT			59940
	AGCTEAGATE					50000
				SSSCAACASA		
	~~~~~~	······································	AGAAAACATT	1,4017111,247	AATAAGATAT	50050
JASALLALAT			ROAGDACATI			50111
			TITIMITAT			50111
02-070032-77	COARRECTTO	9440000TAT	7732377777	4724707003	. 0200000000	35573
ATTRATATAT	ATTICATES	<u> </u>	TAAAATTTTA	RUAA STITAT	*******	30333
3A 2A 3 2 2 4 2 T	1777777	1022027753	T 177 TAX-44 17 1	CTCCCATTAA	STIATITIE	10141
TRUTT 1:4: TT	3004000000	HA30000160	10111104511	777.734.777	TTCTTT.AATC	55-21
AATTTATA	TICATTATT	400000000	7732442377	TTTT::////	ROBORATOOOR	52421
TCTTCCTATC	7707021.300	TOOTTOTICAD	TTTTTACOAT	LAAGTSATTS		30343
ACCETT DAK	PASSTTCCAT	TACACCCATC	Addinotati		778777777	50800
ATTIATTIT	READTORES				TETEKTEKTA	10510
3000			AGDAATDAAD		. TOTTTSASTAS	60720
	101370700		307.32			50780
					TESEATTEEL	50341
3333713311						40300
SGATTATTES			7777777			12743
TTCTTTTT3A3			. TTCCCXCS ::			51.11
3073333333						61030
	1000220					51140
CONANIAST			TTTTTAGAGT			51223
AGAASTITAT						\$1080
TOSSITAAA						51127
SATSARJART				: IXCXIIIII		41393
ACATEATTET			AATSCOTCS:			51447
	. 19999 077 979					SIECO
	. PARTTARTAC					\$ 1, 5 4 7
AAGA IAAAA I		. TOAG AGG 53:				5.5
TANTONGON	. 4555235523	: ITTSAJITT	TACAGECET	: ::::::::::::::::::::::::::::::::::::		51.580
			i otootoekt		T TENTATIATE	\$1740
SCTAACASS:			i adamatat	: 3050 0775 00	C ATSACTACIC	61300
TCAGCATTC		CACCTACAC				61351
AGAACACTT1	: 3 073677 ,67	TACACAGE:	N CONGRESATE	T ACTOASTTS	A TONOSACOTT	61320
CACTITITIES	G GEOTTECAAC	TACCADAMA A	i www.	T TOTTTOCKS	A SCITATICAL	51981
					i stackakata	52040
					A TEMACAGEAE	
AGAATIITA	R GERATTIEN	S DATTTERALLY		: TUTTACALI	T TSTTATETAT	40141
770727333	t kadakaditak	. watetaten	1 11777777	1 37377851	A TOTATATAT	
113131111	3 SCTTEERST			- 144417171	T TAGAGETTEE	42232
	: ::::::::::::::::::::::::::::::::::::	1040047	* 2277277			
					- ' '	
			-		-	

FIGURE 5P

	7,72323,774					
			AGAAACTTAA	STEWATETTT	TATELERIS	
			TTTATTALAA	TTTCV4CV44	ACHAMACTT	5312C
		30.4	SAACACESTS	ACTAACAAGC	TTATTACAAC	53130
	~UC.A.J.J.	JUA	3000000000	***************************************	TESTAGACAT	63240
	~~~~	TATTACTT.	ATSTACSTSS	TAGATAGAAT	TOCKCOMOCT	12300
		A7377CCTTT	TACTTOCAT	ATTTTTALA		63353
0		AGGGTTTTTG				53420
			7000	~		63130
		300000000000	30020000			53540
	A	ACTECT:355				53600
	200	AGTSSSSSS				
AAATTTTTA	************	2247777777	TGATAGTAAA			53660
STEATITIES	1972-1773	GTAGGGGGG	7020773437	~~~~~	***********	53720
TEESACAGAG	3577703407	**********	במונונונוני		C.C.	63780
STACEATETT	30.37.2	22-72-72-7	7007700077	9	Juc. CA.C.	53840
CTSTACTOR		100100000		TUCTTUKCTO	ATACCAGACC	<b>5390</b> 0
1177177777	7,777,177,0	7:777	<del>C13131311</del> 7	GCGGAAAATG	TGATTTCACT	<b>5396</b> 0
			CCCTGACTGC	TETTTERCE	7307373073	54020
	.~~	Constitute	CAACTOSTAG	************	TATACCATGA	54080
3.AACAC.	.~~~	ATACITISTS	COATTOTOTO	TTACLESTTE	CAATACTTAT	54140
		71777			·	
			20020			54250
JUAN	~~-~	.300.00.	11.71777			54320
-~	JUUM	TUNDACTOR	3351477157	71 77 71 71 71	33,00000000	5-111
~	war a constitution of the contract of		* : · · -			5
	~	CTCCTAXCAT	37002400773	73727777		5+51
******			33771		· · · · · · · · · · · · · · · · · · ·	44141
	and the second second	1022177775	ACAMATTACT	73.53.53	11.55	44420
			171711			1+11
375733333	7.3 7	70%070%007	TTTTTATATC	5477177171	TAGAMAGET	44743
ACACITIES	72227227	777326232	1,:-:			44511
AAAATTX230	IACTTCCCTT:	191941111		CATTALALAT		
32 2 2 2 2 2 3 T	33ATTTTTT	TATABBETE	~:		11117X 1145X	94323 94323
ACRONICTES		34737-1-			***	
7773277777	3334733333	3477247111	221		****	54983
and the second second second						45140
3000000000	DAGAGAGTER	300770%007				
ACTIONALITY	TORGORASTS	PATTRATTT			ACCACATOTA	55161
ASACCARATA	RAACTENEE	71440=====	JUNUANTER		*	
23,00223,033	37.20.2000	7777	TONTECTION	200120120		55283
TABLETT SATE	7372577774	155555555	1103111111		400.4.000	55242
AATTTT1311	7773477333	3817518380				55400
3277777377	12711-771-	1010111111	.aua	SAGGTGCCAG	4072273	45443
3711711771	110000000000000000000000000000000000000	Assessment and the second	GGCATTOCAS ATATTOTOS	*******	JAACATALICT	63520
111771717		Addition of the	ATATTTT555	TEATERATEA	3773,737333	65550
122112	2222		ATTACTITAL	ATTTOTTOTA	ANGETTINETS	53540
COLLABORA	730703	AUATEESSAG	JAAGCETTEA	ACTTOCAACA	SGAACUAGCA	4 <b>573</b> 0
202111111			TAGAGAAGAT	313357535%	777733CV.GC	55750
	~					45320
	A.AC.3	<b>~43 1</b> 47 1 143	INAMOTITE	723GC <del>TTTT</del>	COTTANTO	653 <b>a</b> C
~~	スレスレールシスシスシ	100-1100				65343
AC. 33. 2.13A		10000077733	SUCKETSON	20112300000		56000
• • • • • • • • • • • • • • • • • • • •						46343
J	39 <b>~</b>	3043223	7			44122
	~~~~~~~.		~			
		A		~	·	
4 4		33-				
30000000000			,			
			·			
TCACCASTTT	SAGTESASTS	1000011441147	SATSALASSS	7,77777	11.13.1000.0	5 1 5 4 5
AAATT TOTA					week. Ide	,,,,,,,

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	7	,	the state of the s			
C			* *			
	4 - 7 - F 1 - 1 - 1 - 1		- 184 (RD IX III	5555712223	1111111XX-1	67027
J	51 57 NA (No. 1)		- 1 - 2 1 2 1 2 1 2 1 1 1 1 1 1 1 1 1 1	- 000007124445 - 0707010707	777777	67 32 7

FIGURE 5Q

4 777 77773	T TITTAGTAG	N DATESSETT				57250
STEASSTEA	A GTSATETSE:	100570465		3C 2700C . 30		
ACCUTUCCE	S SCHARLAGE	AGGTATTSAC	7777777	- TAGGA - T.NC	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	47323
AATCAGCAA	G Clacksian	: ::========	- 3222	7000070757		57380
	2 22 22 22 22 2	; 3070700755 ; 307077007	J. ANGATT.	ಜರ್ಷ-೧೯೮		57440
	c terretions				7000000	57500
AUAC	- LIACTAGE	: KONOTTOTTS	ATTECTOR			5736 0
mounny.	T TTAGEATTA	TTTTATATAG	JTTTTTTGACA	- 	3007737777	57520
TASATTTT	7 7772 275575	TAATASTTEA		CANATOTEST		575 a c
**********	T INACTACIA:	************	TTTTTAGETE	COCTACTOTE		57740
TATTITTE	: compenses	TETTSAGSTT	STSTSATAAT		TETSTSCTST	57300
ECONTATES.	T AGCENESASE	: ENCATOTARE	7171777		~~	
TGGCTAGTG	ೆ ಜನಗಾಗಿದ್ದಾರ	STACAATTTT	1777117		TTATATATS	57363
SAAATASET.	\$ 2373777 555	TEACACCTOT	1177777	~~	~~	57923
TOCATEACT		STITITIONS				57980
TACTANANA	1711111		7000.000.7	ACATGGTGAA	ACCOUNTED	59040
	J GRAGAGAAT	3000000000	71300/6363	SETSCAATES	CASCTA CT 23	54130
	3 30.00000000.		7300000700	AGGTTGCAGT	SAGCEAAGAE	63150
	CACTICALCE		ACTORCACTO	TSTSCAAAA	*******	68100
AGCCATATT		- TATTOLATTO	SACIGERESS	::::::::::::::::::::::::::::::::::::::	2223273034	33130
TUTAATTTC	. TEAGGETEGE	- TAKTTTOOKST			20077770000	58340
TAACTICTA	GTTTTTTAATT	********	77773333377	TATTTTALL		53400
		7777520000	7347730000	ATSASSST**	13	53463
GATISINA TO	- AGGCTITTAT	AACACCA CTT		TANIGGANCE		
3777773777	: 	ATTTTUACCA		375335755	TACACTTIAC	13121
75222223757	. 55% <u>4444</u> 557		-32 22721 23			11511
22770A755				RURERUTERS		Fig. 1
TT::::::::::::::::::::::::::::::::::::			TATTALAART	REACTROTOR	727777733	3 5 7 7 1
77777		7777171444		INDACTORES	1744114177	44741
ATTAGT INT			7273222714		IAATIAATI:	F 4 4 0 0
3777777	7777777777	_	127111111417	SCHARTSHIR	4-47300377	51111
			00000000000	CONCORACTO	77777777	4440
7723247-77-		7777772020	TOTTTAGAAG	7003037003	TATTELEGIA	43111
703277777	77777742A2	TNT200A,400	3827733773	170.000.0000	42777.7	23.52.5
AATTIMITI.		TTTAGEATEE	3557355735	22273777	ACCOCCACCT	30111
TTGGNGTET.		77 77 77 7 7 7 7 7 X	TOSTTOTES		70077	3/1:1
AGTTA JAJAA	TTIBETTEAT	TEETTHARDS	3335	11777777	3CACCAGGGA	
	ICCASACAC	7777777777	1	GCCACTGCCG		5:14:
DAAT WITTEN	3070237747	WATERTTON.		TITTALTATT	JATESTTTTS	5 3 C C C
4572771447	94 77 4747474	77 24 22 2 7 1 A			STTACATTOT	63363
TT 1211222		· •		ITTESACCE	TOACCTTCTT	13423
773227777	7714.204.34		7237722373	17/12/16/17/27	7037732003	13.51
7237737557				TABASASTTS	YCCMT/YGCCC	535+3
734777777		4400070070	STEATETSAT	400000000	100710000000000000000000000000000000000	43511
701773333		7277772447	500000000	2000000000	7777777777	40440
100000000		7777777474	ACTIACA 2777.0	TERRICOTRO	TODAXABERST	3:-::
	327772777	7014040000	1111111111	III DAWA IA IA	1035005	41731
372723.327	77W377W3	2442 373 37 T	TERSASSTEE	CCCAGACCC	TACTITUAT	4.134.
~ 433 k3 = 7 3 k	4400000000	1A 07 00 0 15 7	CAGATOGAG	ACCACCA-T	JOSATJOSST	4 1 1 1
773 77227333	22732335777	277772333	2222322222			
CAGG+244377	ANTIRUACTI	335575775	-1-1-1-1		771777777	77751 733 2 1
TTTTTTTAKTI	. 4444.744.					70.73.
	73,27,27,2277	WTWETTER.	55 7777 777	W.CATCOAGT		
A	TTTCAGAATT	7777351-	CASTATTTT		CATTOTTON	73.43
ACATOTOCAE	AGATOTATAT		221788	7100000000	STSTSTACT	79200
*********	1272727273					70060
GASTTIATT	ATTGTGTTGG		STTAAASAGA	-	7535575575	70000
14		TEACATETAS	المتداد المتعادد	445545477	CATACCAT	70130
	7					70440
						77500
						**=5
	3	39-AATT NOT N TOTNOCK 200 ATT TO NO 200	PETER CATES	TETAGAAGGA	171377777	7752
						70333
.	7277773424	27777222	NECERTERA	TITTITICT:-		
	*1 * 10					
					filit.	
TT 94 - 14 - 14 -		1 - 1 - 1 - 1 - 1 - 1 - 1	. : . . : : : - : -	- 13-45-13-14		
	- : : · · · · · · ·		1225		erana er	
			- 1			

FIGURE 5R

GAGACTICT GCCTACCTA	T THANGETT	WET WATER	- 03/70 1 0 11	ACCITECTAG	ATTOMATIA	~1460
300.55	·					71520
~~~~~			- AGT1771516			71580
		~	10-0			71540
TTATOCAAT		· ····································	ふこれてコモスモロコ	CATCTCTACA	WATTAWAATA	71700
AATAAATAA		-A-40.335.	777247722			71750
77077777	· ·······	<u>Withing</u>	ROSTAGGETS	CTC/CCTCAC	:CROCKSSTS	71310
190	- ^~~~-		AAGCAATTIT	TOTTGCTTCLG	1770000400	71380
Au	. ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	JETACEACAT		######################################		71940
~~	TITTATTA			<del>11.113.11113</del> 3		72000
	: SGGTACATOT	. 20100110240	CAGGTTAGTT	ACATATOTAT	ACCTETECEA	72063
TOCTOGTEC	5	. דאגכדכנדבג	TETAGEATTA	GGTATATTTC	CONTECTAT	72120
	: terrerowa	CCACAACAGT			**********	12130
CEATSTOTT	: TCX <del>TTGTT</del> C;	. ATTOCCACCT	1			72240
	4.40	GAGAATTAATA	3			72300
			######################################	3000300	3077777	72360
3.30.3004.		AUC - 10 - 10			101101010	72423
AGGACAGAGA	- CACAGACACA		::	~~~~~~~		70480
the control of the						72540
			::	J.L.AGCES	CCCACCCACT	-1533
· • • • • • • • • • • • • • • • • • • •		*******	AATACATSCT	SAGESTSTST.	772777222	72560
TATESTETA	. AACTIACTON	ACAGGETTTT		3777777X77	1373735751	
77.2477777	TT WATTAWA	NOTTO COMPAT	· - · · - · - · - ·		77732777333	-1-11
***********	TOTATRATOS	22 <b>07</b> 3,27 13,2	AATTWITST	2777773067	522227777	7234
			AGAAAGTTTT		777377777	-53-1
407000000		7.77.73.77.73	Notte the term	COCCUTTORS		70940
	11111411111	77777A7	HETERALISI	3823375555	30000	-1::::
		1770 TT 10 1	377777777			12.08.2
300000000000000000000000000000000000000		177123737	7777777723	177/4/27770		11.4
1237:777:			TRATITI	13.13.213.77.7	7077073704	-121
10111000000			7777777		77777777	712:1
77702 27 377	1034033433	777774772X	23777777775	44743 <del>77777</del>	W. W. C. W. C.	
3000000			353,5355553	30.7		72223
TTEATATETA		1777777	*********	7772723272	7037032772	71443
TTTT ITTAI		27.77.77.77.7	3007030300	7.000000377	7777773	73333
	TIBATTABLE	77377777	STITISTITAS	303000000	377777777	73553
IINCIT:30%		IDNATERTAGE	TTTNETTTAL	1577533577		71521
30774111111		TITTALKITAL	1777737	1337523557	225512551	73612
327777777	777777777	TTTNACATRI	SACOTOTORS	13.277.00.101	WCCTCCTC	73747
	200 - 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	47007000%5	PT CALIFORN		CONTTACACO	71301
ENSEASCIAS		TATTATATAT			TORKETTOOK	7135
<b>377 237</b> 33 3 %		AGAMAT 1 1111	DAGADEATTS		7377777777	
TOATTACTAC			NATRO DE CAT	3777373777	773444.773	11981
TATT : 13:17	TATITIATA	777037373				74341
7773737373	7373734427	2 1711117			1113737313	74121
~~ ~~.~ · ~.~	The second second second	ACCTATION.	377273773	20001777		14131
			TTT 5 **** T	AUTTTATOTT	T5/371/37-	
3713710777	ATACTTCT	24242	NOTTT DATES	<b>***</b> *********************************	1777177277	74230
***********		AT 7T 12T Q4 1		227737777	797181181	74343
TTICATTO	CATTOATCAT					14433
AFBATTTOTE	1077773073	7777777722	454454555	TOSTATTAT	TTX T 23.5. TT 2	74461
		*			ATTCCCKCCK	7,020
9-99-11-13-1	ASATTAATTT	TOTOTT OF TH			<del></del>	7.530
77777.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0	TTTAATAATA	AAAGTT E ETK	AASTOOTSAA	1111111111	3372.272725	746.0
J	~	3037777373	TGACTATTSE	AATTIGTATA.	2272273773	74722
_07777773	TESTTETTAC	ATTORAGESAT	TACTAACCAC	\$575\$7 <del>775</del> \$	AATTTTTAAC	74753
AA3TTTT:::T	TTTAAAASTO	20%33357557	TTTTTATTT	WASTETTAGE.	73 <i>7</i> 22722	7.327
7.77777777	3072407080	TT 13.2 = ====				-,;:
307 330 7 777	TTTTTTT					*
	3-0 - 6 - 0		sandonada)	1103030730	17-7-19	
sauda 2000 er e	7	*****				

#### FIGURE 5S

GCCCACAGA	STEASACTET	PTTT TAAAAA	17	TANTANTANT	CATATOCCIA	15660
CTCCTATAGE	- KOTTAGACTO	בגדכדגניגב	ATTACLET			75720
1TT 1.0000	- ************	3777.XX	ATTTATGAGT			75790
STTAGAAST		. AGG				
:::::::::::::::::::::::::::::::::::::::				3202225		75840
32 <b>3777</b> 3323				AMAGETETA		73900
		SAGCACCTEA	TTTSACTTS	JTAGAATATA	3AAATSSAAA	75960
JUATTTAUAT		TT5AGAGGCT	30000000000000000000000000000000000000	IGGACT TITE		75020
SASTTAACA		. TTUTTE 40TT	JCTTTAGTGG	3777777377	ACTTOTACTO	76080
AAAA CATTI	N TTATGGCATT	ATCTACTTA	***********	<del></del>	TATTACAAGT	75140
ATATTTACO	CO <del>CTONIT</del> OTO	ATTEXABLES	7237777747			75200
CONGTANCA	: TTXTTTXSTG		CCAGGCCCTT	773772727		75250
2322347000	: TACTICTING	ATACTATICE	TTTT			
72.	797755553					75320
AAACTECTE			ASTEGEATAA			75380
				AAAGTECTEG		75440
			SATTCASATT	TACAGATGAG	COARTAGAGE	75500
CTTAGGAAGG			TTTATTTAGT	ಸೂತರವರನಾಡಿಸಿ	CCAGGATTE	76560
	TTSAGGGACT		TOURTGOOKS	TOTOATATOO	COTTO	75620
TT 277 777 7	ATECOTORES	ATGATATOTT	707777777		AG****	76630
STTSSACTSS			CTSTSATATA		ATTRACTOCT	75743
722377773		TTACAATTT	III JATUTUT			
	ACCTOCATOR	SAATTATAGT			SCTCCTATAT	76300
757373777			STERRESORA		TOAKSSTITS	75350
707307777			AGGCGGATKT	ATACTTEENT	TTCCCACTOS	75300
		- NATAICCITAI	777777777	TACTTEMATE	773.000073.7	7633
478477777		TOTTA CALASTS	7737377773	ACRECTIVES.		77747
T		***********	4000000000	37.7777777	7777777777	::
	. A <del>ttititi</del> kkii	TAUTET 1 1.4	TITATINALA	:== <del>====</del>	TOMAGEONOT	**11:
75/4577777	HADACITTICAL	ACCTORCOCK	NUTTRITTET		1377575555	****
22220-23753	2000220000	700070000	7772327325		7277734347	1::
11111111	TAN DAN OTTO	3077032703	1041343703			
3 <b>77</b> 737:3:3		%ASTTTSTTT		1111111111111	372777777	
2303773423			TAGEOGRAG	1777252777		,::
7000000000			307111111	131277137	1333127777	
7777777327		ETTATATATA	VIX.CX.CXAXX	HTTTMATITE	111111111111	111
			772777777	7777777	777777777	77533
77537777777	77777777	7777777.00	TTOASITTE	170711111	JGCAGTACAA	77572
AGATTTTTT	777777777	7777777777	::::::::::::::::::::::::::::::::::::::	100000000	307.077.77	::
TTTTTT%T%1	AGATA0122T	77 73 77 77 77 77	772777777			;;
BASSTESSE	2773272777	13,023,000000	TASTOSASTO	1227227	222723,2722	:
44:07777000	77777777	44 SCC4 TT 57	2272227722	12772771357	SETTEENET	77991
ADACOTOTO	2223273777	31,12171,175	77777777			
23.77772222	SUIATIOTIT	1347.171777		TACTICAGAC	W22777	7735
AASTTSTSS	377123227	771777	1211111111	12/12/2007	11.201111111	73000
4772712177		TEASSTAGAS	1117711111	3-40777743	<del>1111</del>	73161
	TAATIOTOT	37727272 <del>7</del> 7	ACADAGETTE	7777347777	340377773	77123
Water at	4003002717	T0808TT187	ACATTTIATA	33.57.534.57.7	ACATETT	73137
	1777777777		TADDURTADD	TOSSTITTT		T3140
EXTERES :	10000000/01	3073477777	TITIIATII	T323377770	777777	79333
₩::	₩A ERSALATT	RTRINGTTTT	**************************************	SATTISTIT		19160
	7 7 7 7 7 7 7 7 7 7	TTTTST	TTTACATCEA	STETSKETST	5523555355	13.21
7777777777	T 507 11 52 7		750.4407700		TOTACOTTO	73,50
ACCONTINUE	<del></del>	TTOTE WEEK	7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-7-			
220074777	<del>111111</del> 7311	7777737732				785+7
######################################		SETSATETS	nenco-os		CTSSAAGST	73630
CATCACCONC			***********		36A 77.46.465	78553
	TOCKCOCCC		1077723572	ACCATASTTC	ETTEGAÇAST	~ : - 2 :
TEATTERACT	TETTOEXTET	47.004.73.00°C	777777777	THE TTE COLOR	TACTTTTTINA	73730
	JETSERTTSE		1,			73340
	~~~ · ~ · · · · · · · · · · · · · · · ·	· · · · · · · · · · · · · · · · · · ·	3727544.717			79900
√~		33337555	44			****;
and the second	And the second		72 77 - 7 - 7 - 7 - 7	:		71323
~	arman man in a contract					
						,
T12772121	77777					73.43
						1 + 1 2 1

		•			
		3175077373	2000/27/00	::::::::::::::::::::::::::::::::::::::	
-	 	::-::	:::-:		
	 			5 to t=	

FIGURE 5T

	A STEERAGES	Contractions				
77327777			<u> AFFAFFFEE</u>		AGAACTTICT	73860
		-	::::::::::::::::::::::::::::::::::::::	TC:\GTTTTC	TT CATETIONS	73920
AATST STTT			JATATTE	:::::::::::::::::::::::::::::::::::::::	AATTTTTAG	79980
TEATAGETE		. Additoxx	AAATSTTATS	221677777	313131111 3	30040
73577772237	. AGAGAAATTT	: ACTTORITE	AAACTETEKT	TTTTTTT	STANTSSATS	30125
	: ACTTCCCTTC				ATTATEATAT	10150
3737735757				TACLASTITA		
ACTOTACOT			TACTATIAT	SGTTCACACN	30777777	30223
			ACTORATETE	TTEXSTTTS	teetetteet	30230
			3102121	STTACSGTEE	5367367777	30140
TOAGACTET			*********	7377377235	AAATTOOTAAA	30400
TTOCKTTOK	: ctactttew	. SECENETERE	727577277	ATENTETTA	TTATTGAGCE	30450
CAACTACACS	, 5 	TOATTATTOT	ATTECANOT		=======================================	
ATTTTTTAAT				TOTATAATTT		30520
ACTTOTTON				ここここくじんじんごん	ATTTOTAATT	30530
			TAAAATACTT	STEATATAAT	TOCASTANCE	30640
AATTERTTT			GCTCACTTAA	AAATAAAAA	TARRAGAC	30755
CTAGACTTT			TTCACACCAA	WATTERSARG	AAAGTAAAGA	30750
STETECEENS	AAAAATAOTA	. ರರರರಗೊರರಲ್ಲಾ	SAACTTEET	323773777	3557373720	30320
CCCACCAAA	· CTINTOTTISA	ATSSTAGETT	7030247777	POSTUTTOT	CCCACCCATT	303ā.
CASTISCAGO		ATSUBUSERA				
ATAACTTTS			ATOTTTOORA	TESTSTITE	ATGATAGTTA	30347
100110000			₩GAGGGG TT	:::::::::::::::::::::::::::::::::::::::	1377277	31200
			727722723	7777773	CATTGCTAG	31151
37577775533	CONTOTOOAA		ATTAXATETE	37 377 37373	TOWNSTACTO	11111
ACTITICIT	AT IT ITTIA		AGAATTGAGT	SATACACTOT	2737234237	11111
	3777073.707	1777777447	COATTAACTT	377773	30000000	1111
5553455555	3782777878	TEASEATTES	2727702727			
IN-ATITUTI	3774447773			7734377477	7232737723	11111
7707 TTT 1265			732777777	TO SAATA SAS	147327777	:
224221222		TITTITIT	4774457777		75,4000000000000000000000000000000000000	12:11
		1777120771	7777777777	TTTAGGATTT	13-145 A 53-11	11,11
0.3. 27		77777244477	74 277 277 2	NOTTROTART	1773777777	313-1
2372777777	1377277733	77 277 % 777	2777.471.275	3738378378	7772377237	#1#11
TT: 14: 17:11	7774477748	7077700337	ATTTTTCAGA	7237377273	777777	11441
TEXTIGATES	7523773532	727727777	777777	77777777		
ATRITUMENA	3477774747	ATTAMMA.TT			TATAAAACII	11711
TTA::::::			TTINGACTTE	100110111	********	31733
*AGTTETTEA		377377337	ATTACTALA	₩ITITIAKI	ACAGENERACA	3.11-1
	ACCOMPTENZA	300702230	ROTTTONITT	COTACCONIC	TINGGACTTE	31311
JAAAA DAA ST	NET TO TELL	TTEETTEEXT	7777773733	2272227737	STITTIONS	31340
200400700%	JAACACTOCK	RESTRICTE	RESERVATERS	4740440444	ACCETECIAL.	32222
SAAL-20000	777777777	10000000	JEACTALETT	1000000000000	733444577	12111
ACAMONYCCA	477,030771	SETTENCACA	CATTACTT	JACTOSTIAL	WEINGTACK	
1012223	444-044-0585	77777777	TTOTIAAACA			321,5
SATTTT STT	77777777	37777775		7777773.275	TAXTAX = TTT	32227
11131111111	327227222	2221		CASTUAUTET	13,57,77,777	12241
		2002470777	SCTTAGTGEA	\$27 77 77777	197955 777 0%	12222
	ATCT ## 1000	TTTTTTATTA	STTESSATTA	13,232137773	1111230311	10030
₩.:=:::================================	127377774	27/ 25 2AT25	33TTTT:A:00%	TETTECEE13	157777777	32-40
AA 27 7 7 7 7 7 2 3	TT TRAKTORT	ETETTESSET	TOCCTTIBLE	~ 377777745	4773024277	30000
TTARTOR	23,22757774	ATTTTTALETT	STTTTTSTAL	TARGTACATA	7777723272	12341
TAGATITICA	ATT:34TTT	1777	SATTTTTT	TTTGAGGTGG	3.7.7.3. 	
CATTRIBLETS	TTTIBATTTA	TAXATITTEE	TANATTAS			32321
	***********	ACATTETTT		TAGTACCTAC	40.0007.000	82687
TOATMACTON	***************************************		SCT CTST CAA	SERCONSTEE	AGTOCOACAA	31740
		IWITCITTO	SCTC.WASTA	TOSTECTION	TENSOTTETT	30300
SAUTHSCTES	PASTATASST	0030000000	1373757555	TAXTTTTTT	7.3 7.77777	92351
TUTACACACA	AUGTETENET	\$75775553	NACTICATION	SAMETERETES	2772347234	31711
*********	TENSTITTEE	AACCTETTEG	CACTTTCACAC	STEASEEAST	2234442770	32355
*********	TTTTTTTTTAL	CATCTCAAAT	7337244.777	TAGGETERTS	3000737373	
TS 22.772.777	TETTERAKTE	MADDETSAGE	324432445			33342
ATTT::::::::	₩11777 ₩4	SACTOTATES		7	TTTASTEAT	30100
ATATTTAATA	3333773277		TTETTATEAL	TTTTATATTT	11117752333	30160
372737177		IAVATITET	7287777777		NTTTACKSTK	40000
	TTACASTT.	TTACAAARIDG	SGAGATTT		TTTTTX5233	3::::
77A 144 7777	THERESE	3750377555	2732237545	1177273313	:3 <i>:</i> ::::::::::::::::::::::::::::::::::	41.14
2777 274224	374747777	344312115	3843547557			

FIGURE 5U

CACCOACCTT	STOTESSERV	AGACOTOBIT	TAACTALAGA		ATOTTACTT	34060
*******		ATTANTANA		ATSSAATTT	 5022473	34120
AATETTAGAAA	AATAMAAT.	MATTERMANT	AATSAATASS	JAAGCTSTAA	TALLATERET	34130
TEAGGETTER	TTCAGTCENT	7734473737	STETUTEACT	AAAATSACTA	4655723724	34240
TTAGACAATS	AASTAAGTSC	ENTAWAT TEA	AACAATSTAA		*******	34300
AAAAAAACTAA	GGAGTTTGGA	DATADDADAG	JOSAGGATST	3772777237	AGTAGGGAAT	34360
TACTTAATAT	TETTINANT	TORAKACATOT	300000000	ACTITIATUA	TTSAAAACTA	34420
AGTTTTTTT	33.T TTTTT	7237377777	TUANGGETAT	TANGANAT	AATATTTAAA	34480
TARRESTERAT	TTSATSTTCK	222777	TUATTTTTT	TOTOTONANT	AAADTAAA	34540
7722473447	ATSTITUTE	AAAAATSSTS	7537777777	TAAGTAAATT		34600
7407737773	772377373	3757773777	ATTENTERAT	CARTGGATAC	ATTTTCACAG	34660
ATAAATGGGG		AGGGGGTGAGA	SGGTATTSTT	TTTTALCTT	AACCTSTSAC	34720
GGGTTGGKTS	AGGCEAATEG	AATCATTTT	AAATSTSTTT	ACCACACTAG	SCAGACACAG	84780
AAGACTSSGG	TITTIACACTT	STSTSSSALS	TOURGROUNT	SACAAAAGGG	CENTERACT	84840
SCTSSSSSA	ZACAGCAGGG	AGGGTGGCTG	COSTSCTSGG	700000000	TTTCCTAGAG	3+900
AATGTEAGGG	AAAGGGATGT	SESSIBATE	CCTGTGGACA		AAGTAGGGGA	84960
GAGGTETSET	ATGGGGTTTT	***************************************	37733ACAGG	######################################	AGAGAGAGGA	35320
TGCCCAAGGA		ACTIGUETIAS	AGGTTTTTA	357247555	ACTTOTSAAT	35380
TTCTCATOGA	AAGCACTAC	ATAATTTTTT	TOCATOAS	AGCCAGACCC	ACCTGGGAAT	35140
TCTAGGCENG	2445447000	TIMETICAL	ACTIGGETICE	ACUTAGETET	SACEATEGAS	35200
AGGTTTTGAA	TTSTAGETTE	5530730365	AGAAGTAGGC	TOGGAGAGAGA	AAGGGGACAG	35260
AGGAACCACA	2000000000	TEACETTENA	ACAGAAGCEA	37222273	AGGGATIGAG	35110
AAAAATATAA	SSCTANATTA	AGTTTTTTTA	TTTTTTTTTT	5773433777	ACTICACCET	35131
CANCETTEET	SECTOMACS	3777777777	277,227777	703073077	TOACTACACO	25-41
23,23,73,03,40	11.71171112			STAGASATAS	197177777	35511
77777777	121711111	AAA2TTTTTT	1071140144	777777777	70.3027727	33341
***********	SATTACASST	3734207377	10111111111	ACTTT WASAA	TTTTACAST	31323
TATAABAA	782878 777 7	4477477177	3773777777	43ACA3ACT 1	77,077,777	::+:1
7000000000	<pre><pre><pre><pre><pre><pre></pre></pre></pre></pre></pre></pre>	10.2012 T 1777	1771/1717	4007004007	-27262777	33747
30000000000		*********	3000000000000	377,22,23,275	IGATTTITTE.	35613
TTTTT::::::::	117777777	AAST TOT TAKE	1713437447		TAGGTTTTTA	353:1
AASTOOTTO	3773333713	3757777037		SENSESTATE	TTT3CT3CT3	33300
AAAST DAATS	44,27,47,477	727377777	SUCAUTETUT	WASTEWAST	CTXTTTSCX5	3 1 9 9 1
20322034207	300000000000	272222222	2272733477		3777A70470	360+1
=======================================	TESTASSASSET	2777377733	33222333733	TCTCTTTT:	400000	3 4 1 0 0
TIRGIRTIRI	IT ICCCC.ATE	AASSSTT SAT	ASATOTASTE	ANISTASAAA	::::::::: :::::::::::::::::::::::::::	36161
COT COLUMN	TREETTREERT	2777277773	373,770,077	3324730032	AAATTTTAGT	36111
INAMAR STOCK	STARCTITAL	TOTALISMA	TOTTTTATAL	TTTTTTTACK	TANATA	35230
4007077077	7777727777	777773333	7724433443	*********		363-0
- NATIOT TO ALIT	423 27007 07	AATESTITCT	3437533333	RESERVEDED	SCACTENAGE	36-00
2877777777	277722777	STOASTAGGE	200A0TA2A2	7727273734	1111111111	36-61
SERETTER.	44 TTTT3TT	TACTORIAGE	7777711747	STRORDERGS	TTCTTTTT:	36327
ASTATTIASI	TINKITINTI	377777	30007773,44	RETECTORSA	TIAGAGETIT	3 6 3 5 3
343171117	ATTEMETERS	377 27 27 277	TTGTATITAT	ATTACTITUT	37337577733	165-7
52424 27773	CORRESPOND	7773.00.00 777	JATJAAAAA	********	11111111111	35700
30322 ETTAA	RETREWASE	ACTINICAN	STOCKERSOT	TTAGGAGAGT	GGEATTT NGA	35751
AUAUAUTAUT	ACASTTOAAS	IAA ISITTIT	TT:TTT::::::	T:::::::::::::::::::::::::::::::::::::	TEACACACTE	36620
CATOTOSTEA	77,577,007,00	STTTTCTSCA	SASSTTBEET	TOOTSSTOAT	ACACTACTET	a 6 a a c
ATTTT:TTCT	PASSESSES	TOSTOSSISS	SSATATOTO	CAGGGGATAC	ATAMAACTEE	36540
ACAMARTICA	40.04377474	GGT SKT KT KA	AF TTT DAGGS	INTESTICAS	AAGGAGAAGT	31200
TOOTAAATTO	TATEALATA	JATITIAUT	ISSAGGSTEE	CRIPATRITT	\T35 \ \\$T\$3	3 7 0 6 0
1310111111	TTSTITAATE	7777371171	7777334447	3523773577	AAGTGAACTT	57123
ATTTTTTATE	TOTACCOCAL	TAGIAMIRTA	4004004000	AA DA OT AAA T	****3*35*35	37137
***	SEATTTAGAA	ACTUATIONA	7737000033	TTGAGGEAGA	TTT13T3171	37145
STETTALAAA	TARAITATIS	TACTACTOR	ACCONCITED	ATTICATOAS	STERBOASTS	37333
TOADAD DADA	TTTTTTT ACK	TOGESTARAS	11231177773	IAAAAATTIA		37153

FIGURE 6

STAT		TT	AGTA	VAT GT	'G AG	GCCT	CTCT	CGA	TGCC	TGG	GTCC	TGGG	CT T	TGGT	TCTCA	60
STCC	rcc.	.TA	AATC	ATCCT	.2 C.	'GGAG	GAGA	λGA	.cccT	TAG	ATCI	GGCT	CT T	CTCA	.GGGGC	120
ATTT	maaa	.GA	CAAAI	ممموء	A TA							CTA C Leu G				171
			EST qrT													219
			GTT Val													267
9 AA 914	770 Phe	007	GGA G17 45	700 Ser	ATT 11e	GTT Val	TAC Tys	AGT Ser 50	TAT Tyr	GAA Jlu	GCT Ala	AGT Ser	GAT qsA 53	TGC Cys	TCC Ser	315
TTC Phe	377 181	3 e s	344 313	3A.3 Asp	ATT Tie	AGC Ser	ATG Met 85	ogr Arg	CTG Leu	345 202	ga£.	333 317 70	TAE qa <i>k</i>	STS Val	gtg Val	263
			i ATS : Met													411
AGA Az g 90	etc Val	gca Ala	. STG 1 Val	ATC Ile	GAG Glm 95	TTG Leu	TGT Cys	STS Val	TCT	GAG G1u 100	AGC Ser	AAA Lys	TGT Cys	TAC Tyr	TTG Leu 105	459
			Ten Ser													507
ota Leu	5 <u>8,4</u> 51,4	A.A.: A.s.:	T AAA n Lys 125	Ser	ATT Tie	AAG Lys	AAG Lys	GCA Ala 130	Gly	GTT Val	GGG Gly	ATT Ile	522 Glu 135	Gl.	GAC Asp	5.5.5
cas Slm	TT5	1,1,7 1,47 1,47	s Leu	erg Leu	OST Arg	GAT Asp	777 Phe 145	q aA	GTT Val	AAN Lys	nn (GAG Glu 150	AGT Ser	TTT Fre	STS Val	603
		ī.:	s gam i Asp				514					: Ala			733 775	65 1
490	37.0	,1,1,	. 331	7773	377	ا جيد	. 0.4.0	. 57 0	: 77.3	. 333		· 0,=_=			3 4,4,4	7. 2.S

FIGURE 6 (CONT.)

GAC Asp	CAG Gla	AAA Lys	573 Leu 205	TAT Tyr	SCA Ala	GCC . Ala	Thr	GAT Asp. 210	GCT Ala	TAT Tyr	GCT Ala	GGT Gly	CTT Leu 215	ATC Ile	ATC Ile	795
TAT Tyr	CAA Glm	AAA 1ys 220	TTA Leu	GGA Gly	AAT Asn	Leu	GGT Gly 225	GAT Asp	ACT Thr	GCG Ala	CAA Gln	GTG Val 230	TTT Phe	GCT Ala	CTA Leu	843
AAT Asn	AAA Lys 235	GCA Ala	GAG Glu	GAA Glu	DAA neA	CTA Leu 240	CCT Pro	CTG Leu	GAG Glu	ATG Met	AAG Lys 245	AAA Lys	CAG Gln	TTS Leu	AAT Asn	831
TCA Ser 250	ATC Ile	TCC Ser	GAA Glu	GAA Glu	ATG Met 255	AGG Arg	GAC Asp	CTA Leu	gcc Ala	AAT Asn 260	Arş Cam	Phe Phe	CCT Pro	GTC Val	ACT Thr 265	<u>9</u> 3 9
750 Cys	AGA Asş	2.2.T 2.3.n	TTG Leu	GALA G1 u 070	ACT The	ono Leu	CAG Glm	ASG ASG	GTT Val 275	CCT 2:0	GTA Val	ATA 11e	TTG Let	AAG 175 230	AGT Ser	98∓
ATT lle	TIN Jer	5A.A. 51.u	AAT Asn 198	oto Lau	TGT Cys	70A Ser	TTG Leu	AGA Arg 290	AAA Lys	GTG Val	A.TO 11:	TGT Cys	3 37 317 295	Pro	ACA The	233
AAC Asn	ACT The	3A.G G1.L 300	The	AGA Azş	ord Leu	NO.G Lys	223 Pro 305	GL_{T}	AGT Ser	AGT Se:	777 25.8	AAT Asn 310	Leu	CTG Leu	TCA Ser	1083
TCA Ser	GAG G1. 313	. Asp	TCA Ser	SCT Als	got Ala	GCT Ala 320	gga gly	. GAA : Glu	ala Dys	. SAG Glu	124 175 325	. Gln	ATT Ile	55.4 Gl:	. AAA : Lys	_131
CAT His 330	Ser	ACT The	TTT Phe	GCT Ala	AAA Dys 335	Ile	AAA Lys	GAA Slu	GAA Glu	CCA Pro 340	Tr	GAC Asp	CCA Pro	. GAA Si.	CTT Leu 345	1179
GAC Asp	AGT Sec	TOA Lev	4 973 1 Val	350 350	Gla	. GAS . Glu	GA:	G GTT . Val	GAT Asp 355	o Val	C TTS	T AGA e Arq	k BAC F Asi	7 C.A. n G1: 36	= 3TG n Val 0	1227
AAQ Lys	; ;;;;; ; Gl:	1 -1) 1 Gl:	A AAA 1 199 369	s G1;	1 624 7 Glv	k TOT 1 Ser	1 3A2 5 511	a AAT u Asr 370	1 51	A ATA u Ile	A GAJ 2 51	a gad Laras	0 AA1 0 As1 37	n Le	G TTG u Leu	2275
AGA Arq	A GAJ J Gl	A GA As 38	p Me	9 923 1 91.	A AGA 1 Arc	A ACT	TG' = Cy 38	s Val	3 AT' 1 II	T CC a Pr	I AG c Se	T AT' = 11 39	e Se	A GA r Gl	A AAT u Asn	1323
ر_ .و	.	n 0.4.	A 5-	7.7	5 GAJ	A 11,21	3 CA.	A 90	. %	A 5A	.	رفرفر المر	A TA	T :	t ter	1371

FIGURE 6 (CONT.)

GAC Asp	TCC Ser	3er TCC	TAT Tys	ATA Ile 430	ATT Ile	GAA Glu	AGT Ser	GAT Asp	GAA Glu 435	GAT Asp	TTG Leu	GAA Glu	ATG Met	GAG Glu 440	ATG Met	1467
CTG Leu	AAG Lys	TOT Ser	TTA Leu 445	GAA Glu	AAC Asn	CTA Leu	TAA Asn	AGT Ser 450	GAC Asp	STG Val	GTS Val	GAA Glu	CCC Pro 455	ACT Thr	CAC His	1515
			TTG Leu													1563
GAA Glu	GAT Asp 475	GLY	CAC His	GGA Glv	AAŢ Asn	GAA Glu 480	GCC Ala	ATC T <u>le</u>	AAA Lys	GAG Glu	GAG Glu 485	CAG Gln	GAA Clu	GAA Glu	GAG Glu	1611
5AC Asb 499	His	TTA Lel	TTG Leu	000 E 20	522 514 495	200	AAC Ash	GCA Ala	AAG Lys	CAA G1n 500	ATT Ile	aar Ast	TGC C∵s	cmc Let	AAG 178 505	1689
ACC Thr		770 20e	3GA 31 y	0A0 His 510	AGC Ser	AGT Ser	Ph.e	aaa Lys	353 215 515	GTT 7al	GAG Gln	TGG Trp	AAA Dys	GTC Val 320	ATC Ile	2707
39.T H13	777 361	273 741	773. Leu 525	57 <u>1</u> . 511	GAG Glu	AGA Azg	AGA Arg	GAT Asp 530	۾ جيد	GTT Val	GTT Val	STC Val	ATG Met 535	λìa	ACT The	1755
335 317	7.2	333 317 540	_ / S	AST Ser	oto Leu	TGC	773 Phe 545	G1::	TAT Tyt	CCG Pro	CCT Pro	TTE Val 550	TAT	ACA Thr	. GGC 517	1903
Ĺ∵s	353	31 j	Ile	Va.	ile	Ser 56)	3:5	Leu	Ile	Ser	Leu 563	Met	Slu	Asp	CAA Gln	1851
370 731	le.	53.5 32.5	omn Leu	92.5 91.1	omo Leu 575	Se:	AAT A∋n	g TT Val	CCA Pib	. GCC : Ala 580		TTA Deu	orr Leu	GGA Gl,	. TOT Sea SBS	1899
GCA Ala	CAS Gla	39% TDN	. A≞A Lyo	AAT Aan 590	. Ile	STA Leu	. 55Å 31y	GAI Asp	0TT Val 595	Lys	TTA Leu	. 650 . 617	AAA Lys	TAT Ty: 600	AGG Azg	1947
STC Val	ATC Ile	TAC Tyr	ATA Ile 605	The	455 ' 619 :	GAC Glu	TTC Phe	TGT CVS 610	s Ser	GGT Gly	' ALAC ' Ash	TT3 Leu	GAT Asp 619	Let	k crc i leu	1995
1.A.G	0.4.4		JAC		AGT	` A.T.	771	3.70	1 407	7 777		7.7	77	; ;:	n man	* .

ing pagamanan na manggalan na ma Manggalan na mangga

FIGURE 6 (CONT.)

ATG Mes 650	oma Leu	3GC 317	TCT Ser	CTT Lau	AAA Lys 655	ACA Thr	GCG Ala	CTC Leu	CCA Pro	TTG Leu 660	GTT Val	222 210	GTC Val	ATT Tie	GCA Ala 665	2139
Ten Sic	T00 Ser	got Ala	ACT Thr	GCA Ala 670	AGC Ser	TCT Ser	TCC Ser	ATC Ile	CGG Arg 675	GAA Glu	GAC As p	ATT Ile	ATA Ile	AGC Ser 680	TGC Cys	2187
TTA Leu	AAC Asn	omg Leu	AAA Lys 685	GAC Asp	CCT	CAG Gln	ATC Ile	ACC Thr 690	TGC Cys	ACT Thr	GGA Gly	TTT Phe	GAT Asp 695	cgg Arg	CCA Pro	2235
AAT Asn	cTG Leu	TAC Tyr 700	TTA Leu	GAA Glu	стт Val	GGA Gly	CGG Arg 705	rhe ww	ACA Thr	GGG Gly	AAC Asn	ATC 11e 710	CTT Leu	CAG Gln	GAT Asp	2253
															3A.A. 31.1	2331
3 31 31.						TGT Cys					Mec					2379
						omg Leu				€∵s					ila.	5 4 27
									ے ق						AGA Aig	2475
			: Gin					Thr					Met		ATT ; Ile	2823
		i,, :					3.1					. A.			3 37A . 314	2571
A.T.: Met 810	31.					n Gli					a Gli				A CTT y Leu B25	2619
5A6 31:	3 431 1 391	: T5:	5 T 57	T CA: 5 Hi. 93	: Le	3 CTC L Let	TGC	g ger p Al.	T CC. a Pr 93	s Al	A GA a As	o TT' p Ph	T AA e Aa	3 A3 3 T A 3 4	A TOO r Ser O	2667
4,3	3 ,2_2,°	77	3 37	î 2.I	T 3A	G AT	I IA		T 5A	a aa	.G T T	5 7		.=	7 AV	. = 14

FIGURE 6 (CONT.)

												TGT Cys				2811
												GAT Asp				2859
												GAG Glu				2907
												GCT Ala				2955
					GGA Gly							777 208 234			55A 917	3003
							ASP					CAC His				3031
39 T 317 310											ی ن	ACC Thi				3099
										Val		: AAG : Lys				3147
				೦೪ತ					_∵s					Leu	5GA 517	3135
			3-21					Sez					فأشأت		944 914	3243
GAG Slu	AT3 Met 103	Ehe	n day Pro	. AGC : Arg	, Alaa Filiya	. GTT Val 104	Let	G CTA	. CCA . Pro	. AGT Sei	TC: Se:	: Asr	con Fro	: GTA : Val	. TOT . Ser	3291
00A 2ro 105	Gil	. ACC : Th:	ACS The	5 CA4 5 Glr	0AT 1 His 195	Se:	TC: Se:	7 AAC Asi	n cad n Gla	4 AA3 7 Aar 106	n Pri	A GC1 o Ala	n ssa N siy	\ TT# / le:	% ACT 4 Thr 1068	3330
ACC #k.		5 C.A.:	777	i ee	7.7	3 5 4.	3 AG	A ĄC	3 C.N	777	I Ţ.Ā:	c AAJ	A ST	3 22	T 9AG	: 3 3 *

FIGURE 6 (CONT.)

TCA CCA GGA ACA TCT Ser Pro Gly Thr Ser L100	TEC AGC CCC TTA Ser Ser Pro Leu 1105	GAA CCT GCC ATC TCA GCC Glu Pro Ala Ile Ser Ala 1110	CAA 3483 a Gln
		GCC AGG CTS GTG GAA GC: Ala Arg Leu Val Glu Ala 1125	
CAG AAA CAC GCT AAT Gln Lys His Ala Asr 1130	AAG ATG GAT GTA Lys Met Asp Val 1135	CCT CCA GCT ATT TTA GC. Pro Pro Ala Ile Leu Al. 1140	A ACA 3579 a Thr 1145
	a Asp Met Ala Lys	ATG AGA COC ACT ACT GT Met Arg Pro Thr Thr Va 1155	l Glu
		" GAA GGC AAA GCT GCT CT : Glu Gly Lys Ala Ala Le ::	
add dot ots tttp gav Ala Pro Leu Leu Gl. 1180	R GTC ATC AAA CAT 2 Mai lie bys His 1195	n TTO TGT GAA GTA ACT AG s Phe Gys Gir. Mai Thr Ge 1190	T 6 TT 3723 E Val
dag Ada gan otth ott Gin Top Asp Deu Dar 1995	n Tod Act Sec AA: 1 Ser Ser Ala Dys 1200	A doth CAC AAG GAA GAG GA Biro His Lys Glu Gln Gl 1205	G AAA STT1 u bys
		D TOA OTO COO CAG TOT GI s Ser Leu Pro Gin Ber Va 1220	
STO ACA TAC ACT OT Wal The Tyr The Le 10	u Phe Gla Glu Ly	S AAA ATG COO TTA CAC AG S Dys Met Pro Leu His Se 1235	5C ATA 3867 er Ile 340
	u Leu Pro Leu Th	A GCA GCC GGC ATS CAC TO r Ala Ala Gly Met His Lo 50 1255	
Gin Ala Val Lys Al 1260	a Gly Tyr Pro Le 1265	G GAT ATG GAG CON GCT S u Asp Met Glu Arg Ala G 1270	ly Leu
ACC COA GAG ACT TO The Peo Glu The Te 1375	G AAG ATT ATT AT p Lys Ile Ile Me 1330	G SAT GTO ATO CGA AAC C t Asp Val Ile Arg Asn ? 1098	on coo 4011 ro Pro
ATO AAO TOA GAT AO	ra tan aala att wa	A STO ATO AGA ATG TWA G	TT COT

132.

FIGURE 6 (CONT.)

Ser	Sly	3e:	Asp 1325	Ser	Arg AGA	Thr	Glr.	CCT Pro 1330	Pro	TGT Cys	GAT Asp	TCC Ser	AGC 3er 133	Azg	AAG Lys	4155
AGG Arg	cgT Arg	TTC Phe 1340	Pro	AGC Ser	TCT Ser	Ala	GAG Glu 1345	Ser	TGT Cys	GAG Glu	AGC Se:	TGT Cys 1350	Lys	GAG Glu	AGC Ser	4203
Lys	GAG Glu 1355	∴_ a	GTC Val	ACC The	GAG Glu	ACC Thr 1360	Lys	GCA Ala	TCA Ser	TCT Ser	TCA Ser 1365	Glu	TCA Ser	AAG Lys	AGA Arg	4251
AAA Lys 1370	Leu	510	GAG Glu	TGG Trp	TTT Phe 1375	Ala	AAA Lvs	GGA Gly	Asn	GTG Val 1380	5:5	TCA Sei	GCT Ala	GAT Asp	ACC Thr 1385	4299
330 317	AGC Ser	70A 3es	TCA Ser	TCA Ser 1391	Met	GCC Ala	AAG Lys	ACC Th:	AAA 193	Lys	AAA Lys	GGT Gl/	offs Leu	777 Pre 140	Seː	4347
TALAU	AT DE	c:: .=	LO GAT	7792	ic ii.	TTT	FTGT	3 700	:T .A.C.	ATCT	TCA	ITCC:	CAT .	i-Li-LiAG)	ratgaa.	4497
NAGA		XTT T	TAA	33 7 33	ua ad	-TTA	TT3-2	R AGI	rcca	AAGT	GAA	GCT C.	taa 1	TALA	CGTCGA	4467
GCCA	LTAGA	kgt :	7777	- <u>-</u>	311 00	GTT:	330,40	3 TT (3AGC1	TACA	GTA:	rcrsz	l ac	2 77 2	IGAGAC	4527
ccs	JAGT:	30A. (SCAT:	AGA DI	IS TO	BAAG1	703G(ITT:	== = =	ndog	ATT	500 T 1	cc	JAAC	cc st sm	4587
CACT	GT C	433 1	TTGC.	4.GT 01	T T	TCT:	CTT	J CA:	3C.A.G1	TGTG	TGT'	rggaj	-AT	GGAG	GCTGTG	4647
TCG	7777	IAC 3	ATAT?	.	CA GA	AT DA	STAJI'	I TG	CATA	3GGA	CAG	ATAT'	3AA	GATN	CAGCES	4707
STO	7773	777	CTT	.TSC	4.G .A.T	gggg	FGTA	T SA	CAGT.	ATCA	GTG	CACC	4 60	೦೦೩೮	CCAGGG	÷767
AGA	3.5.7.0.5	4.90 t	Tod:		:	- 2,2 -										170

FIGURE 7

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in electrical design of the control of the control

FIGURE 7 (CONT.)

actmattactigeggcacgcctctccacagagtttaccagaaatgtattcataaaatga angunaratiacitteetgitatatttatteesaataatattgitattttattgiatag itttttgctattqtaaatatattttqactctqccctaatttctqaggatqcattqtcat accadaaaaaaqttttattatadttictattqtqttttatadqtttttatadadtttcta attoasaccatottactqttttattatcaattqaaaaaaqaqctactttttaaattataq actocttocttotctqqttataaacaatqqtatobaaataaaaccatttaccactqtqt onontabababagaaagaagaaactgacttossaaagrigototgtdatoccccacqC atdrotcstddtgqqaqcttqctqqcattcsaacataaacatatcacaaacqcscscsCa rugacagatactotototototodoacatocagagagagagagattttcagtatttcagtatt gaagtottq3gagaccaaaagaaggttttacsctaaaaaggaacatttttaattatcccct ctgtttcctttttgaagacttgtaatataattacattatagttaaaactgtagcaatcac agateacacacggaagatgccctgatagcccagaagtagtagcatgaaacaatgtttaatta atgetetetetaacteteaaataataactaatagtactaacagagcagatgagagcttttaa rngtuttttgäääätättttalalaladatttayteatatteaaagetgtetatätgättg şsaggaattilacatqtctcctctttaayyaaacagaqactctcttagctttaagggcttl gtgcccttgqtaatccatqtaaqggqcctqaactqctgcacaacagttggttgtaaaqaa diffittacactiocsagogagacactootootgotgtttuctaccacttgattacaaaaat suttitot at aat aat t attavat aaaa kii oosut sandat gaadaotaaccatussiin oo аа бал эрэл бас үүү эараал ба<mark>ддар</mark>ага нааст заураст, үрүг<mark>аат о</mark>л түүндаг gt ct capgttg cot caacaq cocaacat ababbbbaqaaaaaqqqqqaaqqqact qt carof ili Banoncaotal doggo aaaaaaan bag<mark>oagtingaaaq</mark>ooa tooring<mark>ootac</mark>asadobap notocccussossosstocctocctcasqtccusscasactusecaeecatqcqaqatqcccc ş nada citba 4ş nita i 19693-en et eaggiştict ila şa balga it şişat g<mark>ygqqqq</mark>si it billi , quat ça a zon zuca cabayan 40a0a0 taça cabaqqaa aan anontuaaaa tuca 280 a tataat of tatotattattattat gript gagt gript gagt agadadat poostagdat soonat caactit;ptqqaqttqcttctttttttttataccttttctatgattttqaqttttcaattca adtesessesetatqdaqttaataesettatetataqqqqtateteateadeqqssaaa sauthettotteataatactessigteaataadateaanggesctautaaaaactetaaant satataaattatatatatatatatatatatataattataatta nn nath paga ta tachasat tako tagga na na adusa6 ta tatta taratsa toa haki i n agot ak ni ili uz ya zi at ani zaco adan az ni agot anon hadi zi ni iztigegi. gatin i ntaotutaacaaacaagaterootaagaaagaagattiitusutusaacaaykgokeeteet taattqqttqttattaccaattttaattaaactaaqaattttaaaattacataactttqaaa udador toorn trisactaaggarrititettitrieri ed. bedaaredaateetagaartusu su tiff(as, ui(si(ui(si)) si(si(ui(ui(ui(ui(ui(ui))))))))) + si(ui(aá á d á a a a a á á á á á a ciú agc á á á **a d** a agc ciúi sa tiúi agc agt ciút ciút á á át Quit ag gai 40. uqaaaaattii oo qaaqqaatanatqqattaqaa aabaaattaqaqqaaaqatttaaanti atttaaaaaaaariitattatatatgcatgcaatigtgtittaaatgtgtgtorgtorgo... t pat tietat pag tia tig tiga tiggicia gitigotico tiggia gotica o gotigotica ga tieta gotia go Tagaagtiitisaasttaggtagaaasttittaasiitiinaageishiittetageeessaadata otggtiiltataaatataaatttacotttaaattotottottottottpgggggtatotagatooaast ntgta: btaagaagatatttaaaattaaaataatactgcpgtbn: bcacagetgccpantag tiaeniaganni sugintacti deacattan punaadsabahakatadotttigiaaaa pattonifactgass.ctsucthicidatattius.caqtaatatattitaqqqaxsuss salaunt ar non ar 4a chéasta talàta a taranna l'agair an bharat ar ar ar ar ar ar ar ar

FIGURE 7 (CONT.)

scraggrapaccargaacgggaacagraggrattgagaaaggggaggaagaaagc adaaggt cacattgggcattgtcttagttaggcttactatcgttgtgacdadacacaaää taaaattttacpactttqaqttcat actocatoactgtgggaaqtcaqaqcaggaactctaqgcaggaactgaaggagaggccaa ggaggaacactgottactggotttotottoatggottdotcagcotgttttottagacac pla la acaucet de cet que granda est la cetta et qua de caque e est con actual et uatatatuaaqaadatqtoocacatgotttotttaaqqocaatottataqaqotqtqqqa agobacatgtgccgttgcagagtggcaccggctactqctggctaccacqcataaqtttgg acaaacaaacaatgtgtacatatgcagtaaagctttttqccaactcactqcctggccccq ycatqttaatgaggtactgagaatataaccaarcagargtgagacsrqcaaatgaggtat gataatqaggttctgtgaggtactgagagagagtagccaatcagatgaggaacatgcaaa tgaggcatagtgcataaccaatccgtgtgtgagacacqcctctcctaggcctatataagc $agcaccag {\tt TICT} gggct {\tt Cag} ggtct {\tt Cttt} gcctct {\tt gcaat} {\tt caag} ctctcccag aa {\tt ggatc}$ cigilgcaccategiletigciggicaagicayyeqaqcacaaataqaqectittttii titittaaarigagagteeeteeteetaatgacteeegessysyssaggtggacagtaaa ctagocaggacagatgacccccttgtcaacttggcacaccagtacttattatgaaaacst adoctitocotttttqttcatttttaaqqtctcatattaatattafaatatafaacfafaa ataactttaaaagtttcatattctttaaaaattcaaaaatttacaagttaagtcaagt ada a far cosada tototota a a a tocca a dototototo qua a tancosa que cosa ta a atggatortrongradaartsadatsaattottottottotosaagaagaagaagaag gcacaccacagaaaaattuttaaatgcacartaanaacqaaattaacataataccccatagc gonatinion@00ggeonatocoacawaggoustiniti.sattanggin.com/thuris çacaacacacacactqtqtcacattqqcaaaaatctaccaacaaaggsttqaaaccaagaa gqctactpqqqataqcaqqqctcaaqqqactqqqqacttoctcattacqqaqaaataqqqq ataggaaqaqaaaccqclaaaaaaadtttutttttaaaaatcctactaaaaaccttaat catotatatatataaaaaaqtaaatacaacaasttatacatotataattottataatot nttgactforuntadtggnthtqaäanottggcsasasagcsacttsscosttaacsgtto taaattgotttagagtttataaaaacorgosttttsacattagattgtsttattacattaa aqttqqqtqqatctqqqqaaqaqttacactafqfananqqaaftcfjaaaqaaccqaqqaaaa .Taaatusgtactitaarttiintoatganaacadaaqtticaacaddaaactiftcoaaa acacatttaaactttactussuacaacaacatttaggtaacaagaactttssggangtof gaggaştırışılaşılqçıtıtaqtataaaaccatataqqılaqıraqıraqatatcattic taaddadalaataatattiqaagtotoataataattuaagnu tyyyntanannooddddagaal... tiaaaaactaataacaanttaagagaaaaaatsatsobacaaasootttottotogagaaa tytotottactcaqccaaqaacacactdaaadqonntacqantqqasskotattatatin Fidamem (Apprilitationiamithalpamiaesi), Estantisciuthagicabiti ataccocacagagagatgataattatacagaaaan maaacangcocaaaaatgtaatacon o acata.tamaggatoctqttcattaaqqadansedaattannin hillisaaggabcaaab tatacacataacatattagaattttgaaacaqqqaattaataqaaqttaatttqttata aaaqqalqaaqtaatgtatagttaataaqtqqtttaaqqccttotccttoaqqctaqator mataactiatactaaatatgtatuttutttcaqootaggtatcatatcotacacgaaat anghanghandittoaggitagaigchatannonnachtananahanattidittosi icagoootatotatagaagkingtuhotgagooohootatoaaaasattotootaatotat jatadatatiqtttattggaacttqcaddusqgcafftfaaacauaaataaddaab tadaaaa caachto <mark>acha caa</mark>dagaaaa thiis caa saat gaa taa ista har accaadtu aaa 137 pt por a radaaqaaaaqataattottoottoattoatranttottoottoatoristoottotototootaatotnooni Avanis oo oo oo oo oo oo oo

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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FIGURE 7 (CONT.)

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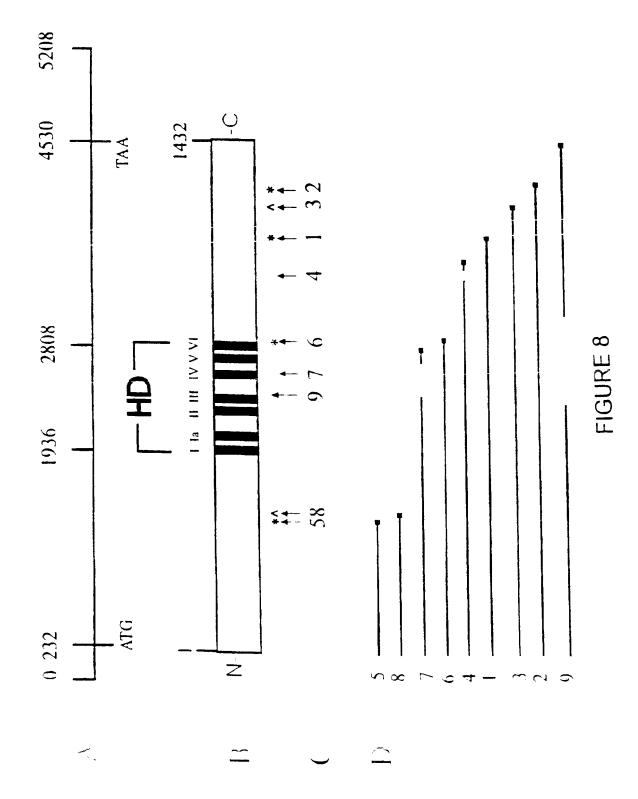
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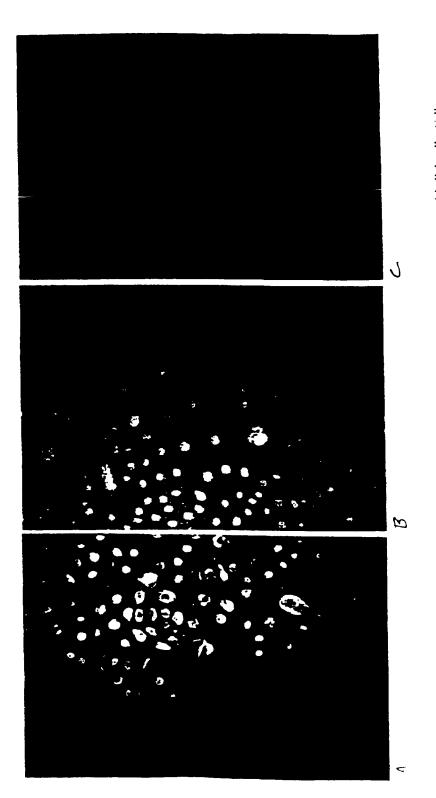
FIGURE 7 (CONT.)

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man prostate epithelmun were plated on a plass slide and allowed to poor for several days before staining. The cells were ace after staining with an appropriate dilution of the anti-WRM js prode trafibut) antiseum. The secondary antibody (goal agged with LHC. Panel B. Hinness cince in the rear infra violet after staming miclear DNA with bis benzimidine. Panel ection of the WRN protein by indirect immunofluorescuce in adherent human epithelial cells. Cells ized, and stamed simultaneously for the WRN protein, DNA in the rockers, or E actin in the cytoplasm. Panel A: nce arising from F actin stancel with BODIPY tagged phallondor. 200X magnetication

FIGURES 9A, B and C

FIGURE 10

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FIGURE 10 (CONTINUED)

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FIGURE 10 (CONTINUED)

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Ir ational Application No PUT/US 96/20785

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Electronic d.	ata base consulted during the international scarch (name of data base and,	where practical, search t	erms used)
с восля	ENTS CONSIDERED TO BE RELEVANT			
Category *	Citation of document, with indication, where app	srupmate, of the relevant	passages	Relevant to claim No.
X	EMBL SEQUENCE DATABASE, 30 January 1995, HEIDEL XP002032088 F. BOUILLAUD: "Study of	expressed		2,15,16
	sequence tags in adipose accession no. T39125 see abstract	e tissue 1995	11	
X	EMBL SEQUENCE DATABASE, 29 May 1995, HEIDELBERG R. BERRY ET AL.: "Gene- tagged sites (STSs) as t human gene map" see accession no. R58879 see abstract	-based sequen the basis for	ce	2,15,16
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X Furt	ner documents are listed in the continuation of box	: C.	Patent family member	s are listed in annex
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•	IPC(6) :A61K 48/00; C12N 5/00, 5/06, 5/08, 5/10, 5/12, 5/16, 5/22 US CL :435/240.1, 240.2, 172.3, 320.1; 424/93.21; 935/62					
	According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED						
	ocumentation searched (classification system followed	by classification symbols)				
U.S . :	U.S. : 435/240.1, 240.2, 172.3, 320.1; 424/93.21; 935/62					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched						
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE, APS, bystander#, migration, msc, mc, gene#, dna#, cdna#, rna#, mrna#, gene, thera?						
C. DOCUMENTS CONSIDERED TO BE RELEVANT						
Category*	Citation of document, with indication, where app	propriate, of the relevant passages	Relevant to claim No.			
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X Further documents are listed in the continuation of Box C. See patent family annex.						
* Special categories of cited documents *T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention						
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